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is entirely absent, the corresponding site of the trigone does not develop. The possibility of an ectopic location of the ureteral orifice must be considered in all cases of congenital anomaly of the upper urinary tract. The solitary kidney presents a hazard in that it is frequently the site of disease or trauma.[10] In 350 cases Hennessey[6] noted associated genital malformations in 33 per cent.

The clinical diagnosis of renal agenesia has been used too loosely and inaccurately. More complete study of the history and examination of the patient in many cases will reveal an aplastic, hypoplastic or atrophic kidney on the affected side. When the trigone is present on the side on which the renal shadow and ureteral orifice appear absent it will often take surgical exploration of the loin to establish the diagnosis of renal agenesis. Furthermore, if more careful microscopic examination is made of tissue removed from the renal area, the percentage of aplastic kidneys will probably increase at the expense of the group of congenitally absent kidneys.

By renal aplasia we mean scanty or defectively developed tissue of metanephric origin which has never developed any renal function or has undergone degeneration during fetal life. There is no true kidney; the pelvis and renal pedicle are missing. The ureter is incompletely developed, often not patent. Grossly there is little of the organ to be seen. It usually consists of an amorphous mass of fibrous tissue in which scattered cysts, some of which show calcification, may be embedded. Occasionally, however, the aplastic kidney may be large, cystic and palpable, as reported in 2 cases by Mertz and Wishard.[11] Its identification must usually rest upon histologic study which shows the presence of rudimentary renal tissue.

Clinically aplasia is usually symptomless but Sabin and Smith[12] have reported 2 patients, MacKenzie and Hawthorne[13] 3 patients and Ainsworth[14] 1 patient who had pain due to an aplastic kidney and who were relieved by nephrectomy. We feel that exacerbation of infection in an aplastic kidney will also cause fever and general malaise. The etiology of the pain in these cases is obscure. It has been said to be due to tension of the obliterated ureter, pressure of the cystic bodies on surrounding tissue or to the tension of accumulated fluid. Most of the 16 patients with aplasia reported by Nation[5] had hypertension, but it could not be determined whether this had any connection with the anomaly. The diagnosis, like that of agenesia, may be suspected upon failure to demonstrate a functioning kidney with an absent or very small lumbar shadow or upon the presence of a blind-ending ureter, and the presence of an enlarged kidney shadow on the opposite side. It can be definitely established only upon gross and microscopic examination of removed tissue. Treatment is not necessary unless symptoms are produced, and then it consists of nephro-ureterectomy.

By renal hypoplasia we mean a kidney which is essentially normal in structure but diminutive in size, from one-third to one-sixth the normal size. Rarely is it bilateral, as reported in the cases of 22 year old men by Graham,[15] and by Murray and Sandison,[1] and in a 13 year old boy by Baurys [16] The upper half of a double or bifid kidney is often hypoplastic The external configuration is usually that of a normal kidney The calyces are usually decreased in number and size, elongated, blunt, club-shaped or otherwise deformed The pelvis, in comparison with the amount of renal parenchyma, is usually enlarged The vessels of the pedicle may be normal but are often diminutive in size

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[10] Fortune, C. H.: Ann. Int. Med., **1:** 377, 1927.

[11] Mertz, H. O. and Wishard, W. N. Jr.: J. Urol., **63:** 959, 1950.

[12] Nation, E. F.: J. Urol., **51:** 579, 1944.

[13] MacKenzie, D. W and Hawthorne, A. B.: Surg., Gynec. & Obst., **46:** 42, 1928.

[14] Ainsworth, T.: South. Med. J., **29:** 619, 1936.

There are no pathognomonic symptoms of renal aplasia or hypoplasia Often there may be no symptoms referable to the urinary tract, the diagnosis being made on routine urological study or autopsy They may exist and cause difficulty at any age Hypoplastic kidneys are subject to the same diseases found in normal kidneys, and the symptoms are the same Chronic pain in the loin is a frequent symptom as noted by Mallard,[17] Hawes,[18] and Graham [15] Higbee[19] has noted the development of hypertension in two patients with hypoplastic kidney Not infrequently it is quite difficult clinically to differentiate acquired atrophy from hypoplasia or aplasia when superimposed pathological conditions exist, such as inflammatory processes, obstructions or disturbances in circulation, so that the final diagnosis depends upon histological sections

Physical examination may reveal tenderness in the flank, an abnormally large kidney on one side and no palpable kidney on the other, or nothing Cystoscopy may reveal ureteral orifices normal in size, number and location, but often the ureteral orifice on the affected side is obliterated, particularly in aplasia It must be noted that a voiding cystogram may demonstrate a dilated ureter and atrophic kidney mass when cystoscopy has failed to do so Reliance upon the appearance time of a dye, such as indigo carmine, is a grievous error in the estimation of renal function The hypoplastic kidney will excrete phenolsulfonphthalein quickly and in good concentration, but a 15 or 30 minute collection will reveal an abnormally poor output in quantity of urine and in per cent of dye excreted This will depend, of course, upon the degree of hypoplasia and the presence or absence of disease in the kidney

The correct diagnosis may depend upon the pyelogram alone and this may be confusing With aplasia one may see no kidney shadow in the plain roentgenogram, but in hypoplasia there may be a small kidney shadow in marked contrast to a large kidney on the opposite side Pyelography will, in the case of aplasia, reveal a blind ending ureter, if present, and in the case of hypoplasia a very small, usually cone shaped pelvis with absent or rudimentary calyces, often with a bizarre shape The ureter usually runs in a straight line with the superior calyx The pelvis may be dilated with a thin capping of parenchyma

The recognition of the presence of a hypoplastic kidney is very important and of great clinical significance not only because of the complications to which it may become heir but also because, if the opposite kidney is removed, the infantile kidney does not have enough capacity for undergoing functional hypertrophy to sustain life. Several instances of removal of the mate with fatal results are recorded in the literature.[20, 21]

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[15] Graham A P J Urol , **60** 580, 1948
[16] Baurys W Guthrie Clinic Bull , **17** 120 1948
[17] Mallard R S J Urol , **46** 216, 1941
[18] Hawes G A J Urol , **42** 500, 1939
[19] Higbee D R J Urol , **51**· 466, 1944

CASE REPORTS

Case 1. F. S., a 34 year old white woman, complained of general malaise, vague abdominal discomfort and frequency of urination. The general physical examination was negative, and the blood pressure was 118/72. Laboratory findings were normal. Intravenous urograms revealed no evidence of any renal shadow or elimination of dye on the right side. The left renal shadow was enlarged but the kidney appeared otherwise normal. On cystoscopy no orifice could be detected on the right side of the trigone, bladder or urethra by intensive searching and probing or from elimination of indigo carmine. We felt, however, that the patient did have a non-functioning kidney on this side inasmuch as the trigone was present.

Operation was performed. Lying against the psoas muscle at the level of the first lumbar vertebra was a small amorphous mass of tissue with a small thin ureter running down to the pelvis. Attached to its upper portion was the adrenal gland. This infantile structure was freed up from fibrous attachments and from a very scanty blood supply and removed. The specimen weighed 10 gm., measured 7 by 2 by 1 cm. and in it were considerable amounts of calcification. No recognizable parenchyma or true pelvis or calyceal system was seen on cut section.

Microscopic examination showed no recognizable renal parenchyma, but there were tubular structures lined by simple columnar epithelium. Some of these were surrounded concentrically by dense fibrous tissue, and there were some scattered blood vessels. This specimen was taken to represent an aplastic condition of the kidney with vestigial structures (fig. 1). The patient has felt greatly improved since removal of this rudimentary kidney.

Case 2. Mrs. M. A., a 36 year old white woman, complained of intermittent chills and fever and of pain in the right flank of several weeks' duration. Aside from slight tenderness in the right upper quadrant and a temperature of 102 degrees, the physical examination was not noteworthy. The blood pressure was 124/74. Laboratory studies revealed: 1 plus albumin, a few leukocytes, a few Gram-negative bacilli in the urine and nonprotein nitrogen, 24 mg. per cent. A plain film revealed a ring-like calcium density in the region of the right kidney. Intravenous urograms disclosed a normal left kidney, but no renal shadow or function could be detected on the right side. On cystoscopy by searching and probing of the right side of the trigone, bladder and urethra no ureteral orifice was found, and after injecting indigo carmine none appeared on this side. It was felt that she probably had a small infantile kidney with infection and calcification.

On exploration of the right renal fossa a small saccular mass, weighing 43 gm.,

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[20] Eisendrath, D. W.: J. Urol., **33**: 331, 1935.
[21] Geraghty, J. T. and Plaggmeyer, H. W.: J.A.M.A., **61**: 2224, 1913.

was found lying adherent to the peritoneum and firmly attached to the adrenal gland This mass together with 6 cm of a small, very thin ureter which was patent was removed There was a very small pedicle in which there were a very few fine vessels which seemed to be almost obliterated On section, it was found that the kidney was converted into a thin sac markedly constricted in size No cortical or medullary elements were recognizable in the wall of the sac (fig 2, *A*)

Microscopic examination revealed the presence of considerable scar tissue, and there were remnants of tubules, some of which appeared dilated The saccular space in the kidney was lined with a thin layer of low cuboidal epithelium and supported by dense fibrous tissue stroma Foci of calcification were surrounded by dense hyaline and collagenous connective tissue No glomerular elements were recognizable (fig 2, *B*) We felt that this probably was a case of hypoplasia in which pyelonephritis with marked scarring and atrophy of the kidney substance had occurred Following the operation the patient's temperature and urine became normal and she lost all her discomfort

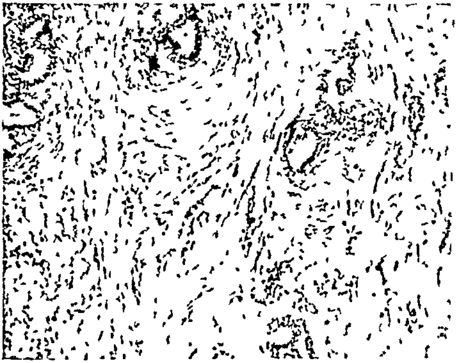

FIG 1 Case 1 Photomicrograph of section from specimen Note tubular structures surrounded concentrically by dense fibrous tissue Aplasia of kidney

Case 3 M T, a 58 year old white woman, complained of headaches, high blood pressure and intermittent urinary tract infections Investigations elsewhere had revealed no ureteral orifice or renal shadow demonstrable on the left side General physical examination was negative except for her blood pressure which was 192/94 Laboratory studies were essentially normal except for a staphylococcus infection in the urine on one occasion

Cystoscopic studies revealed normal urine and pyelogram on the right We found no evidence of a left ureteral orifice, but the trigone was developed Intravenous urograms revealed an absent shadow on the left side with no elimination of the dye, but we felt in view of the patient's history of chronic infection that she must have a non functioning kidney on the left side

At operation, lying attached to the peritoneum in the lumbar area was a small fibrous mass with a small, thin ureter running down into the pelvis Closely attached to it was a normal appearing adrenal gland. With difficulty, this amorphous mass was separated from the peritoneum and surrounding tissues and with a portion of the ureter removed (fig. 3, *A*).

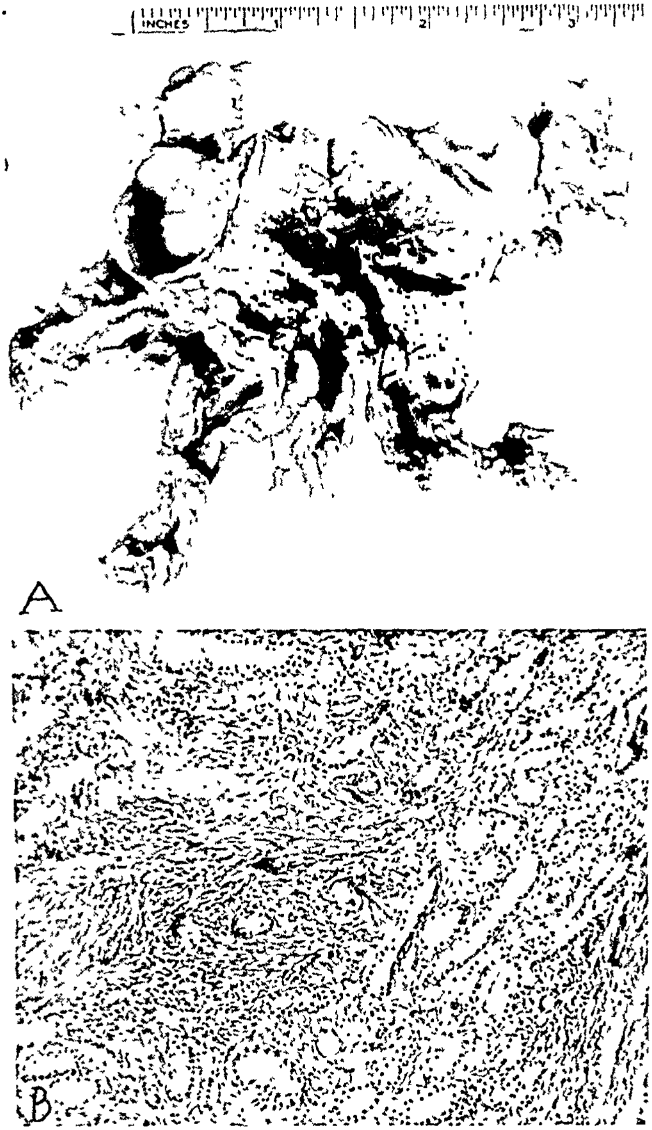

FIG. 2. Case 2. *A*, gross specimen, hypoplasia of kidney. Note large cyst in upper portion and dense amount of fibrous tissue. *B*, showing dilated tubules and fibrous tissue.

Sections taken through the irregular mass of tissue showed no grossly identifiable renal structure and cross sections of the cord-like structure revealed no grossly discernible lumen. Microscopic examination revealed no evidence of any organized kidney, but in place of it, there were tubular structures consisting of a small or slightly dilated central lumen delimited by simple or stratified cuboidal or columnar epithelium. This in turn was supported by a thick layer of moderately to poorly cellular fibrous connective tissue forming a more or less concentric arrangement about the epithelium No structures suggestive of glomeruli were seen (fig 3, *B*) Our diagnosis was aplasia of the kidney with vestigial primordia Since her surgery the patient's urinary infection has not recurred

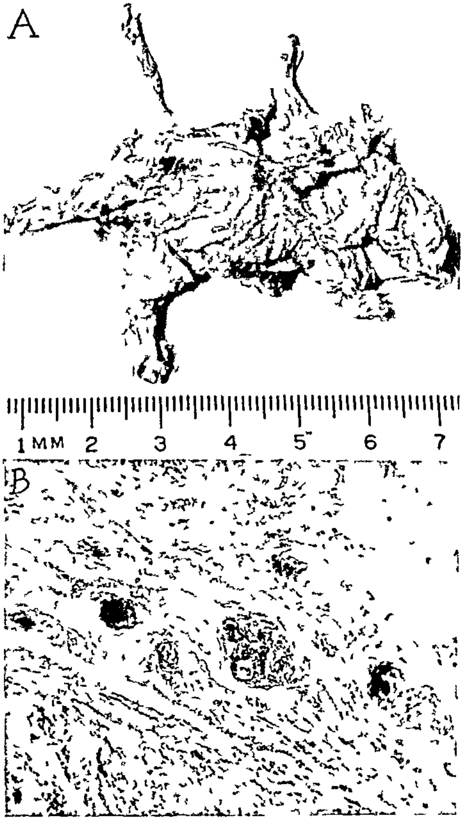

Fig 3 Case 3 *A*, gross specimen Weight 8 6 gm 10 cm cord like ureter removed but cut across in study (Diameter from 0 5 to 2 5 mm) *B* photomicrograph of section from specimen showing tubular structures lined with cuboidal or columnar epithelium surrounded by fibrous tissue in concentric arrangement

Her blood pressure decreased slightly but then ascended to the preoperative level

Case 4 S M L, a 27 year old white girl, complained of recurrent urinary tract infection, discomfort in the lower left side and occasionally pain in the right side Except for a palpable right kidney the physical examination was normal. Her blood pressure was 112/68. Urinalysis showed faint trace of albumin, a few leukocytes and a few Gram negative bacilli. Intravenous urograms disclosed reduplication of the right kidney and ureter, the double ureters extending down into the bladder. On the left was a small renal shadow with a small renal pelvis and irregular calyces (fig. 4, *A*).

On cystoscopy two ureteral orifices were seen on the right side and one on the left. Double ureters, a double pelvis and a double set of calyces were outlined on the right. Only one ureteral orifice was found on the left, and a retrograde pyelogram on this side revealed a rounded kidney pelvis with rather slender calyces, the inferior calyx being very small, compressed and deformed. The suggestion of an inadequate number and the deformity of the calyces in the lower pole of the kidney indicated that there might also be a double kidney on this side Operation was advised for the removal of an infected, non-functioning upper half of a bifid left kidney.

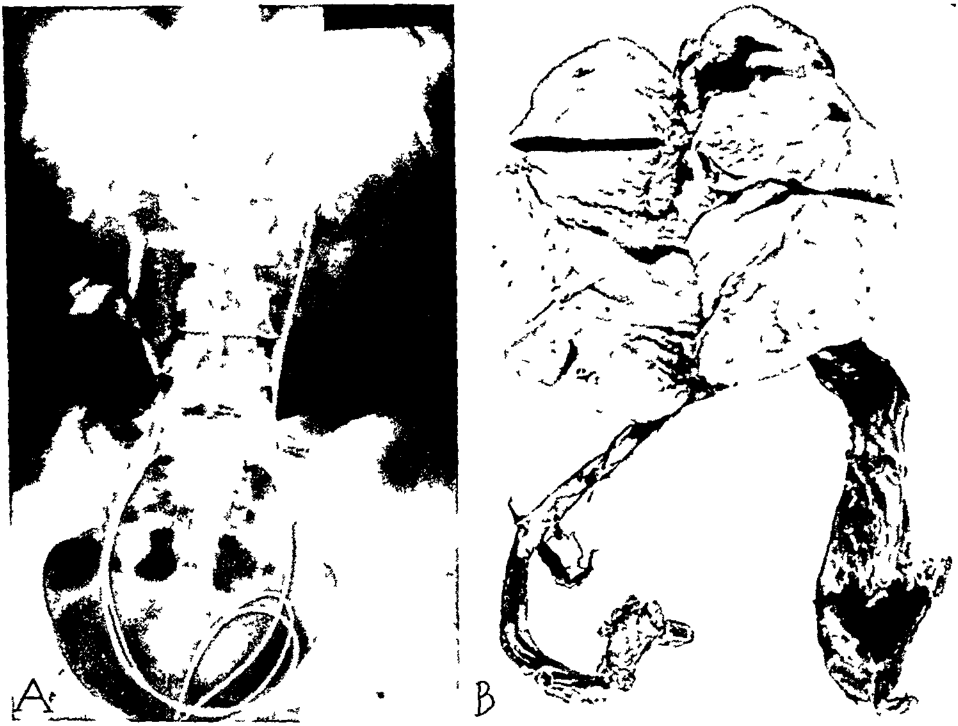

FIG 4 Case 4 *A*, pyelogram, only one ureteral orifice found on left side. *B*, gross specimen showing dilated hypoplastic upper half of left kidney

On exposing the renal fossa marked inflammation was encountered, and in addition to the ureter demonstrated on the pyelogram there was a second very widely dilated ureter, about 2 cm. in diameter, which extended to the atrophic upper pole of the kidney. The lower half of the kidney appeared chronically infected, and consequently a complete nephroureterectomy was done, removing the bifid kidney and the double ureters down to the bladder through two incisions (fig 4, *B*). Pathological examination revealed complete atrophy of the superior pole of the kidney, this portion having been reduced to a mere shell while the lower portion was relatively thick. Our impression was chronic atrophic pyelonephritis in a bifid kidney, and congenital double ureter with chronic ureteritis, bilateral. We felt that we were dealing with an inflammatory process producing atrophy in the hypoplastic upper pole of the left kidney. The patient was discharged from the hospital feeling well.

Case 5. A. W. R., a 49 year old white man, had been treated for recurrent bouts of urinary tract infection causing dysuria. His blood pressure was 165/86. Laboratory studies were all normal. Intravenous urography disclosed no evidence of any renal shadow or function through the left side; the right kidney was found to be enlarged but otherwise quite normal. Cystoscopy revealed that a catheter could be passed no higher than up to the middle portion of the left ureter. Dye injected into the ureter was visualized up to the fourth lumbar level after which it flowed back into the bladder. We felt that his recurrent attacks of urinary infection were caused by an infected, rudimentary nonfunctioning kidney on the left side.

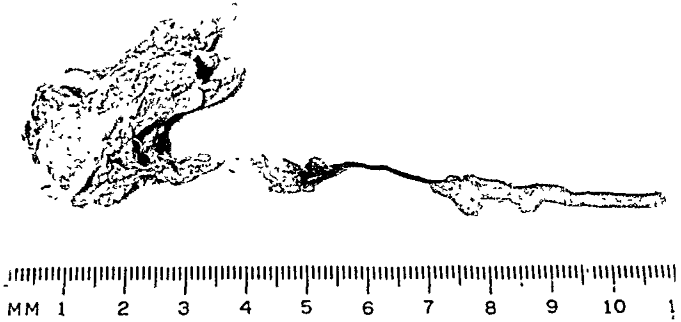

FIG. 5. Case 5. Gross specimen; aplasia of kidney. Note thinning out of ureter in upper portion. Weight 4.8 gm.; 8 cm. ureter removed.

In the lower portion of the renal fossa at operation was encountered a very small, triangular, fibrous structure to which was attached a small thin tube, apparently a ureter. There was also a small pedicle with tiny vessels, but no pulsation was felt in any artery. This mass along with 8 cm. of the ureter was removed. No adrenal gland was noted in the loin (fig. 5).

On examination no normal parenchymal structures were recognizable. Cross sections of the ureter revealed a barely visible lumen. Microscopic study of the mass revealed small cystic spaces lined with cuboidal epithelium, many thickened blood vessels and tubular structures containing dense hyaline, pink-staining material as well as a few cystic spaces lined with tall columnar epithelium with pale cytoplasm, all imbedded in dense fibrous tissue (fig. 6). There were no recognizable glomerular structures. In the section taken from the hilum were many blood vessels but no evidence of thrombosis. A section of the ureter disclosed normal surface lining and slight lymphocytic infiltration beneath. There was nothing in the sections to account for an acquired pathological lesion, such as injury to circulation or obstruction to the ureter or evidence of a chronic pyelonephritis. Our diagnosis was aplasia of the left kidney. Since surgery he has remained free of infection.

Case 6. L. J. E., a 40 year old white man, had been feeling chronically ill and running a low grade fever for several months. He had been thoroughly studied by his physician and nothing was found to account for his fatigue, malaise and low grade fever. Several urinalyses had been quite normal. The physical examination was negative. His blood pressure was 126/78. Laboratory studies were all normal. Intravenous urograms finally made revealed no evidence of a kidney shadow or of elimination of dye on the left side. On cystoscopy no ureteral orifice could be found on the left side, but the trigone was present. By searching and probing the left side of the bladder and posterior urethra no orifice could be demonstrated. Injection of indigo carmine revealed no excretion from the left side. We thought that he had an infected rudimentary kidney whose ureter would open up intermittently and pour out some pus which would cause his fever.

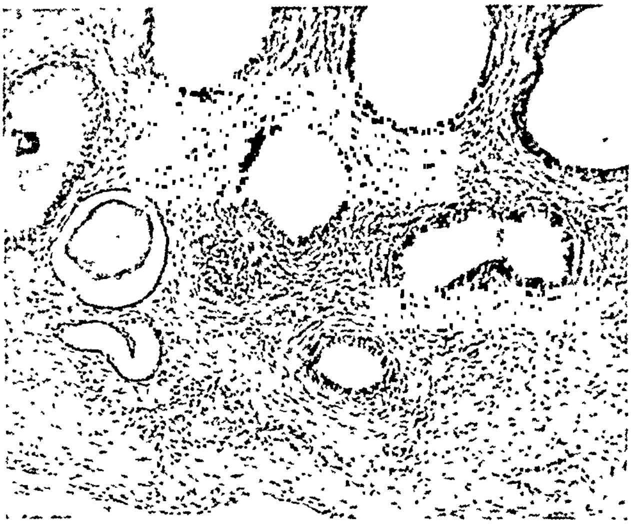

FIG. 6. Case 5. Photomicrograph of tissue removed showing dilated tubules and fibrous tissue.

At operation no kidney was found in the renal fossa and there was no evidence of any adrenal gland, but lying densely adherent to the peritoneum in the lower lumbar area was an irregular, flattened mass of brownish tissue, and from it extended a thin tube suggesting a ureter passing into the pelvis (fig. 7). A cross section through this tube revealed no visible lumen. No renal parenchymal tissue was recognizable on gross examination. On microscopic examination most of the tissue consisted of widely separated simple tubules supported by stroma, in part fibrous and in part mixed with smooth muscle bundles. The tubules were mainly the seat of cystic dilatation and were lined by epithelium ranging from low cuboidal or serous type to tall columnar or stratified columnar epithelium with pale-staining cells containing ill defined minute vacuoles or scattered fine granules (fig 8) It was felt that many of the tubules had a superficial resemblance to tubules of the seminal vesicle and epididymis A cross section of the cord-like structure had the appearance of a poorly developed ureter There was transitional epithelium and ill defined muscular layers separated by scant fibers from the epithelium and the adventitia at the periphery This case resembles the case of renal aplasia in a 30 year old man described by Cecchino, Yates and Chappell[22] in which vestigial epididymal structures were found The patient got along well after surgery and his fever disappeared He improved in strength and vigor and has been able to work without great fatigue

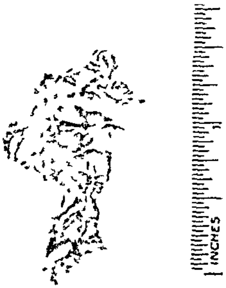

FIG 7 Case 6 Gross specimen, aplasia of kidney Weight 3 gm

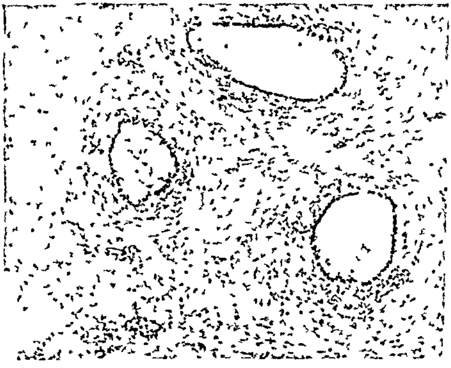

FIG 8 Case 6 Photomicrograph of tissue removed showing dilated tubules and fibrous tissue

Case 7 M G, a 37 year old white male (patient of Dr Robert H Greeley of Marysville, Calif, through whose courtesy the case is presented) underwent urological investigation for dysuria and terminal hematuria Bladder urine and urine from right kidney were positive for tuberculosis. The right pyelogram was normal except for slight calyceal dilatation. Left renal shadow was absent and no function obtained through this side on pyelography. The left ureteral orifice could not be catheterized. It was believed that a non-functioning, tuberculous left kidney was present. Study of the specimen showed no tuberculosis but extreme hypoplasia of the kidney (fig. 9). No adrenal gland was noted in the renal fossa. Microscopic examination revealed no glomeruli but considerable fibrous tissue in which large, dilated, cystic tubules, some of which contained hyalin casts, were seen.

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[22] Cecchino, F E Yates, T M and Chappell, B S J Urol, 66 667, 1951

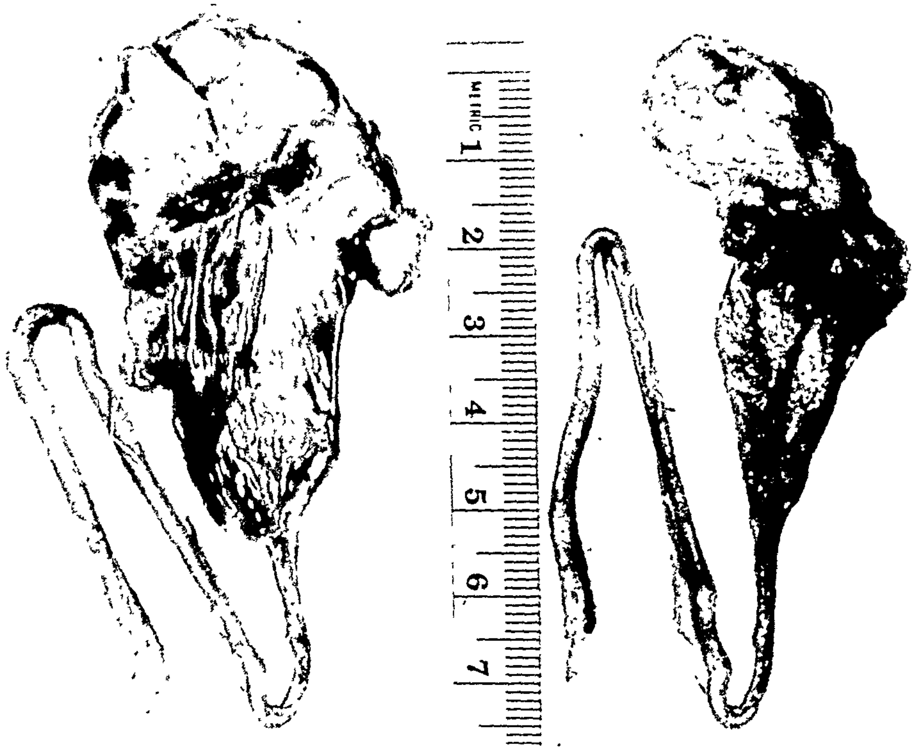

FIG. 9. Case 7. Gross specimen; marked hypoplasia of kidney. Note dilated pelvis and patent ureter; weight 3 gm. Dimensions 3.7 by 2 by 1 cm.; ureter 13 cm. in length and 0.3 cm. in diameter.

DISCUSSION

The most thorough urologic investigation, which includes cystoscopy, chromocystoscopy, plain roentgenography and intravenous urography, cannot completely rule out the presence of an aplastic, rudimentary, hypoplastic or destroyed infected kidney with an obliterated ureteral orifice on the so-called "absent side." Why these rudimentary or infantile kidneys should cause some patients difficulty is hard to explain. With blind-ending ureters Engel[8] has attributed the fever to be due to the presence of infection in them and the pain to arise from hyperperistalsis and/or spasm of the ureter. Several writers[11, 14, 18] have recorded the presence of cysts and calcification (usually in the cyst wall) in aplastic kidneys, as seen in two of our cases. It is felt that pain may occur in these patients from tension due to the accumulated fluid in the cysts or from pressure on surrounding tissues, such as nerves, and the fever from an exacerbation of infection in these devitalized structures The pyuria present in cases of hypoplastic or atrophic kidneys with an apparently stenosed or obliterated ureteral orifice can be explained on the basis that though the ureteral orifice may only be detected by microscopic section, it may intermittently allow the escape of pus into the bladder In such cases methylene blue injected into the ureteral stump has been recovered from the bladder shortly after operation, which definitely proves that a communication existed between the kidney and the bladder, explaining the pyuria"[23] Hypertension has been noted in a few cases of hypoplasia and aplasia of the kidney, as in three of our cases, but the recorded observations are not of sufficient duration to indicate what permanent relief of the hypertension can be expected In our cases, while the history and excretory urography suggested the diagnosis, and thorough cystoscopic examination confirmed or aided it, surgical exploration was necessary in most instances to establish the condition with which we were dealing

It is often difficult to differentiate urographically between the kidney that is diminutive or rudimentary because of some congenital non-development, and the atrophic kidney that exists as a result of an acquired pathologic process Even after surgical extirpation of the specimen, disease may have so altered the structure that the diagnosis is of great difficulty or even impossible upon microscopic section

While pneumography and lumbar aortography in the future may help us diagnose more cases of the rudimentary kidney because of the diminutive size, weak blood supply or absent vascular pedicle, most of them will probably be discovered only by surgical exploration

SUMMARY

Rudimentary, aplastic, hypoplastic and atrophic kidneys may be present in patients despite the absence of a renal shadow and demonstrable ureteral orifice They may exist and cause difficulty at any age

2901 Capitol Ave , Sacramento 16, Calif

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[23] Dourmashkin, R L and Light H Am J Surg , 50 348 1950

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FATE OF HYDRONEPHROTIC KIDNEY: (AORTOGRAPHIC AND RETROPERITONEAL PNEUMOGRAPHIC FINDINGS)

GREGORY S. SLATER AND JOSEPH MANDELL

From the Urology Section of the Surgical Service, Veterans Administration Hospital, San Francisco, Calif.

When a ureter is ligated what happens to the blood supply of the kidney on that side?

It is well known that hydronephrosis follows obstruction of the free flow of urine from the kidney.[1] Hinman[2] has demonstrated that partial ureteral block invariably leads to hydronephrosis and that even a complete ureteral block usually results in the production of a hydronephrosis. It has also been demonstrated[3] that the hydronephrotic process, by mechanical pressure, damages the kidney from the fornices to the periphery. The radial circulation (interlobular and arteriolae rectae) is damaged first and later the circumferential (interlobar and arcuates) circulation. However little has been reported regarding the gross blood supply to the hydronephrotic kidney. The case presented here clearly demonstrates the effect of the hydronephrotic process on the vascular tree of the involved kidney.

CASE REPORT

V. R., No. 52,824, a 30 year old, single colored nulliparous female, was admitted for the first time July 15, 1952, VA Hospital, San Francisco.

She complained of intermittent, knife-like, nonradiating, nonmigrating right lumbar pain accompanied by chills and fever. This pain occurred on two occasions, the first in 1949 and the second attack in June 1952. She gave a past history of tonsillectomy in 1938. In June 1945, she had a hysterectomy. (Two months after this operation, ascites developed and required paracentesis on two occasions.) No other history of past serious disease, injury or operation.

Physical examination revealed no evident pathological change except for a slight tenderness in the right lumbar area on deep palpation. The right kidney was not palpable.

Laboratory examination revealed 4–6 white blood cells per high power field in the urine; albumin negative; sugar negative; urine culture, Proteus, A. aerogenes; paracolon bacilli; red blood cells 4.4 million; hemoglobin negative; phenolsulfonphthalein 30 per cent in 15 minutes (catheterized specimen from left kidney); chest x-ray normal; x-ray of spine normal; excretory urogram revealed normal appearing left upper urinary tract and a non-functioning right kidney (fig. 1).

The patient was admitted to the hospital July 15, 1952. July 24, cystoscopy

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Accepted for publication December 5, 1952.

[1] Smith, Homer W.: The Kidney. New York: Oxford University Press, 1951, pp. 881.

[2] Hinman, Frank: The pathogenesis of hydronephrosis. Surg. Gynec. & Obst., **58**: 356–376, 1934.

[3] Hinman, Frank: The Principles and Practice of Urology. Philadelphia: W. B. Saunders Co., 1936, pp. 491.

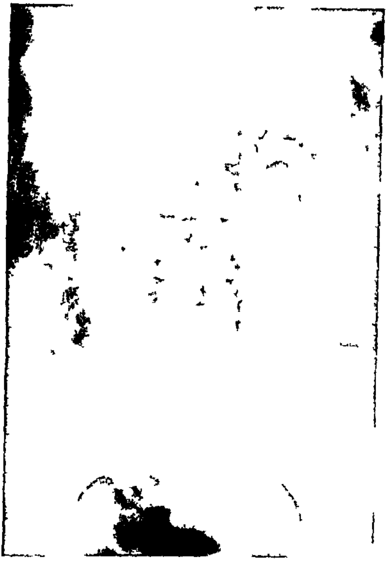

Fig. 1. Excretory urogram showing left upper urinary tract and nonfunctioning right kidney.

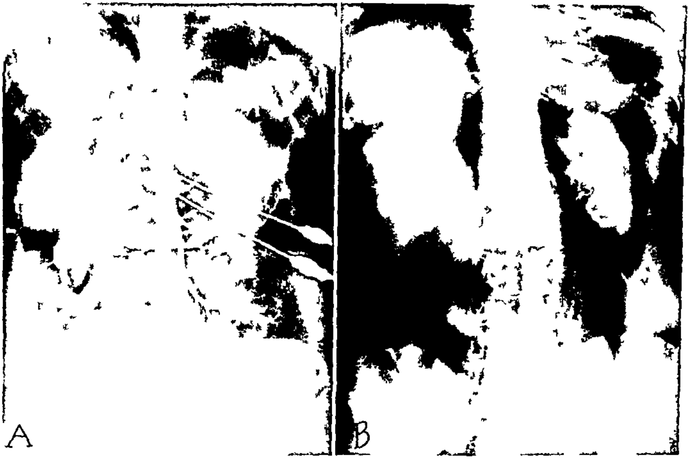

Fig. 2. *A*, aortogram showing blood supply to left kidney and left nephrogram but no right renal blood vessels. *B*, retroperitoneal air insufflation (note clear delineation of left kidney with no distinct right renal outline).

with retrograde pyelo-ureterogram; left upper tract reported as being normal with the urine obtained from the left renal pelvis clear on microscopic examination. A ureteral catheter could not be passed higher than 2 cm. above the right ureteral orifice due to an obstruction. July 31, translumbar aortography revealed a normal vascular pattern of the left kidney with no vessels going to the right kidney (fig. 2, *A*). August 12, retroperitoneal air insufflation by way of the anal coccygeal approach revealed a normal left kidney with poor visualization of the right kidney presumably due to disease in this area (fig. 2, *B*). August 19, right nephrectomy revealed a large multicystic hydronephrotic right kidney (fig. 3) with a hydro-ureter.

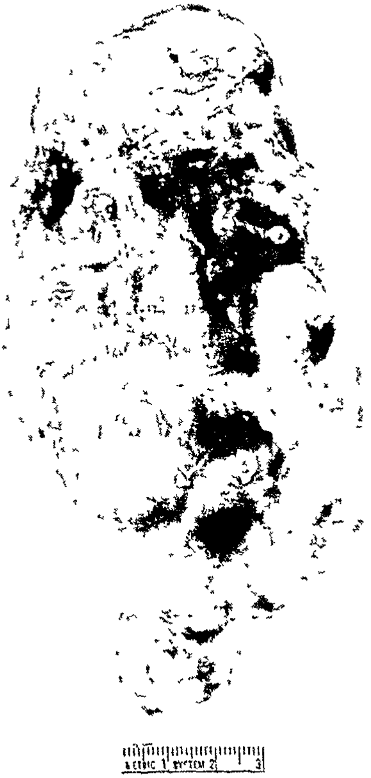

FIG. 3. Hydronephrotic right kidney. Gross specimen

DISCUSSION

This case illustrates that the blood supply to a nonfunctioning kidney probably diminishes to an extent necessary merely to carry on viability of the remaining renal tissue. The kidney no longer performs its excretory function and therefore the great volume of blood passing through the normal kidney is not needed.

CONCLUSION

A case is presented illustrating that the blood supply, including the main renal arteries, to a hydronephrotic kidney is greatly diminished.

2000 Van Ness Ave., San Francisco, Calif. (G. S. S.)
655 Sutter St., San Francisco, Calif. (J. M.)

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RENAL CYSTIC DISEASE

EDWARD WILLIAM WHITE AND LEO BRAUNSTEIN

Renal cystology has been a subject of paramount importance to urologists and pathologists for many years, not that cystic surgery and cyst management present any great problems in diagnosis, but the pathogenesis and embryologic development of these cystic formations are quite fantastic and appear to the authors as a constant urological imponderable.

From a review of the literature it becomes apparent that little unanimity of opinion exists as to the origin of many cystic conditions of the kidney. From these observations have arisen various theories in reference to the etiology of renal cystic disease, each having its proponents and adversaries. Our objective in this presentation is to present a more modern classification and some illustrative cases.

A small percentage of cysts are easy to classify on an etiologic basis, to wit, the parasitic cysts and some neoplastic lesions with cystic features, however, by and large, the majority of these cysts still defy understanding and therefore accurate grouping.

A considerable amount of information, factual and theoretical, can be gleaned from the literature. Some of this has been condensed in the many textbooks on urology and surgery, but one must still consult medical literature for a more complete investigation of this subject and some appreciation of the perplexities which this entails. We mention this not to belittle the efforts of those very able authors and teachers, but to emphasize the vast amount of data that have accumulated and for which there is no space in the ordinary text books. Even in so limited a field as renal cystology, which presents only a small phase of urologic uncertainties, one is soon bewildered in an academic and investigative maze; hence our desire to find a convenient streamlined, authoritative classification. The common denominator to use as a basis for this classification would be the etiologic factor, as we shall demonstrate.

In all the classifications presented in the literature we note a similarity, in that none are based on a single factor. Some are simple, lack detail, others are more complete. Most are not acceptable because of not having a uniform basis of grouping. As a result we detect a sense of confusion and inconsistence.

TYPES OF RENAL CYSTS AND THEIR CLASSIFICATIONS

Under this heading we shall discuss the various types of renal cysts, consider their salient features, and finally place them in their proper categories, as they appear to us after a careful study and survey.

Regarding *polycystic disease* of the kidney, there is general agreement among competent observers[1, 2, 3, 4, 5, 6, 7] that this condition is not only congenital but

Accepted for publication November 4, 1952.

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[1] Kampmeier, O. F.: Surg., Gynec. & Obst., 36: 208, 1923.

[2] Gordon, G. R. and Trisoff, A.: Am. J. Med. Sc., 194: 112, 1937.

[3] Cannon, J. F.: Ann. Int. Med., 27: 610, 1947.

[4] Lambert, P. P.: Arch. Path., 44: 34, 1947.

possesses a hereditofamilial feature and is therefore probably transmitted by defective genes. It has been found in stillbirths, infants and adults, usually bilateral, rarely unilateral. Although there is agreement that the condition is congenital, the exact point of origin in the embyrologic scale is still obscure. Once it was thought that the etiology was due to failure of the walls between the convoluted tubules and connecting tubules to atrophy, with subsequent retention of urine. Lambert[4] showed that these cysts can collect and excrete urine. Kampmeier[1] demonstrated that in the third and fourth generation of the division of the ureteric bud these diverticula do not atrophy, but become cystic and persist as such in the definitive organ. His theory has gained much support.

The occurrence of concurrent anomalies with polycystic kidney disease deserves mention. Sorrentino[8] reported this condition in five fetal monsters. Its association with congenital aneurysm of the cerebral arteries has been noted.[9] Lambert[4] found four cases in his group of seven. Pessin[10] found two cases of multiple cysts of the ureters. Accompanying cysts of the liver and pancreas are not rare occurrences. Renal hyperparathyroidism was noted by Bass and Pakter,[11] while Stewart[12] reported tuberose sclerosis of the brain and rhabdomyomatosis of the heart. Meningocele, spina bifida, polydactylism, and other congenital malformations have been found co-existent.

The so-called *solitary cyst* or simple cyst has created more speculation than polycystic disease. It is referred to as simple cyst, serous cyst, unilocular cyst. These have been considered at various times to have been of neoplastic origin, congenital defective development, or acquired. Those that have been carefully studied grossly and microscopically and found to contain adenomas or carcinomas have been removed from the simple serous group and placed in the neoplastic category. Others have been found to present evidence of inflammation and obstruction and have been assigned an acquired origin. The simple, serous cyst is a thin walled cyst of variable size, the largest reported containing 12 liters of fluid.[13] It is lined by a simple layer of low cuboidal epithelium, which secretes fluid. The epithelium may be flattened by increased intracystic pressure. The epithelial lining is supported by a thin capsule of loose areolar tissue which contains the blood vessels. This cyst is usually found at the lower pole, sometimes at the upper, occasionally on the anterior or posterior renal surface, or in the hilum. Usually this type of cyst is single and unilocular. Cysts of this gross character have been found singly in each kidney, or multiple in one kidney or both, or multilocular.[14, 15, 16, 17, 18, 19] Virchow attributed their origin to intra-

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[5] Oppenheimer, G. D.: Ann. Surg., **100:** 1136, 1934.
[6] Nolan, L. E.: Urol. and Cut. Rev., **49:** 734, 1945.
[7] Yardumian, K. Y. and Ackerman, M. A.: Urol. and Cut. Rev., **47:** 147, 1943.
[8] Sorrentino, M.: Arch. Ital. di Urol., **15:** 533, 1938.
[9] O'Crowley, C. R. and Martland, H. S.: Am. J. Surg., **43:** 3, 1939.
[10] Pessin, S. B.: Urol. and Cut. Rev., **43:** 729, 1939.
[11] Bass, M. H. and Pakter, J.: J. Mt. Sinai Hosp., **4:** 882, 1938.
[12] Stewart, D. T.: New Zealand Med. J., **38:** 19, 1939.
[13] Cassioli—quoted by L. E. McCrea: Am. J. Surg., **60:** 330, 1943.
[14] Higgins, C. C.: Ann. Surg., **93:** 868, 1931.
[15] Grove, J. S.: J. Urol., **23:** 661, 1930.
[16] Russell, J. J.: Ann. Surg., **101:** 1279, 1935.
[17] Kretschmer, H. L.: J.A.M.A., **95:** 179, 1930.

other disease is found the cysts are acquired We object to the corollary on the ground that the cyst may have existed prior to the onset of the superimposed renal disease Burrell[32] added one of his own to the 12 he found in the literature and expressed his belief that they are embryonic in origin Dakin[33] found a unilateral multilocular cyst in a young child Lieberthal[34] reported a solitary multilocular cyst of the renal hilus We shall adhere to the thesis of congenital origin for multilocular cysts and classify them as a type of simple, serous cyst

The next group, which has provoked much comment and speculation, is the *hemorrhagic cysts* Various theories as to their origin have been presented Ten years ago Herman and Strumia[35] offered the suggestion that a careful microscopic examination of the walls of the cysts be made, as many may originate from a renal artery aneurysm or hemangioma We are in accord with this view, and proceed a step farther to express our opinion that there are no hemorrhagic cysts Although we place them in our group of cysts of vascular origin, we felt that eventually, as more causes are assigned to their origin on an acquired pathologic basis, we no longer will use the term "hemorrhagic cyst" as it is a misnomer Many cases already reported have been found to arise from aneurysms, and hemangiomas, traumatic or spontaneous apoplexy of a renal vessel, infarct, embolism or infection may have a role in their origin

Lymphatic cysts of the kidney morphologically resemble lymphatic cysts elsewhere in the body These cysts are lined with endothelium and are found in *intimate association with the renal veins in the kidney hilus Their average size* is about 1 cm and they are usually multilocular Vascular atresias are found in *the newborn, from this observation we feel that these cysts are congenital in* origin and may continue to grow to clinical proportions after birth as the cystic hygromas sometimes do

There is a group of *cystic dilatations* or cyst like cavities in the parenchyma of the kidney These communicate with the calyces or renal pelvis and are usually associated with inflammation and obstruction of the ureter, pelvis or calyces In some there is a defective musculature in the walls of the portion from which they arise These may be classed as diverticula and are similar to diverticula in other hollow viscera, an obstructive element may or may not be present If the condition is traceable to the calyces, it is sometimes referred to as hydrocalycosis, infection may be present or absent The obstructive element is contributed by extrinsic or intrinsic factors involving one or more calyces

In the *infectious processes* involving the kidney, the end result may assume the form of cystic spaces filled with serous fluid or sterile pus The walls may contain calcium deposits or the contents may be calcific The lining of the cavity is not epithelial in nature, hence they truly should not be classed as cysts The walls are composed of fibrotic tissue and represent organized exudate These are seen following suppuration with abscess, and in tuberculosis The small multiple cysts seen on the surface of a kidney in chronic nephritis are based on inflammation and obstruction. This condition is of interest mostly to the pathologist, and is clinically insignificant.

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[32] Burrell, N J J Urol , **43** 656, 1940
[33] Dakin, W A J Canadian M Assn , **42**. 531, 1940
[34] Lieberthal, F J Urol , **42** 365, 1939
[35] Herman, L and Strumia, M Trans Am Assn G U Surg , **33** 11, 1940

The next to be mentioned is the neoplastic group. Here we encounter difficulties as opinion varies, whether to regard these as simple serous cysts which have assumed malignant qualities or whether the neoplastic lesions were present in the cyst wall from the start. It is reasonable to consider them as neoplastic if the neoplastic lesion can be found, and to leave them in the class of serous cysts if a neoplasm cannot be found. These cysts may contain serous or serosanguineous fluid. As noted before, one may find more than one simple serous cyst, one of which may present a neoplastic lesion. Another type of neoplastic cyst may be the angioma. Hemangioma and lymphangioma have been found, and the former may be of the capillary or cavernous type.

We have remaining for our final consideration a group of cysts whose etiology is unquestionable. This is the *parasitic group.* Diagnosis is confirmed by finding the parasite or its larvae. There are three types, the echinococcus or hydatid, the encysted larvae of trichina, and the cysticercal stage of tapeworm. Only the first is of significance to the urologist. In this form, the invader locates in the kidney, develops a cyst, in which is found the daughter cysts and hooklets. If the cyst communicates with the calyx or the renal pelvis, these will be recovered in the urine. It is estimated that about five per cent of echinococcal infections locate in the kidney. It is possible with the present rapid modes of travel, and commercial and military expansion, we may see more of these cysts than formerly.

From the evidence presented and from the observations and works of others, as of our own, we have derived the following classification of renal cysts, based on an etiologic grouping. Realizing that there may be some departures, changes and additions from previous similar essays, we nevertheless feel that an attempt must be made to modernize the subject, and accordingly present this order.

Renal Cysts

I. Congenital or developmental
    A. Polycystic disease
    B. Serous cysts (solitary, simple)
        1. Unilocular or multilocular
        2. Unilateral or bilateral
        3. Single or multiple
    C. Lymphatic cysts
II. Obstructive
    A. Diverticula
    B. Parapelvic
    C. Hydrocalycosis
III. Neoplastic
    A. Cystadenoma
        1. Simple
        2. Papillary

- B Cystadenocarcinoma
- C Angioma
    - 1 Hemangioma
        - a Capillary
        - b Cavernous
    - 2 Lymphangioma
- D Dermoid

IV Vascular

- A Hematoma
    - 1 Spontaneous
    - 2 Traumatic
- B Aneurysm
- C Embolism
- D Infarction

V Inflammatory and infectious

- A Pyogenic
- B Tuberculous
- C Chronic nephritis

VI Parasitic

- A Echinococcus
- B Tinia
- C Trichina

CASE REPORTS

We have selected a few cases at random from a large series of renal cysts collected over a period of 25 years We feel that they should be of interest from a roentgenologic and pathologic viewpoint Such salient features as symptomatology, differential diagnosis and surgical management have been omitted

Case 1 A K (478862) was a woman aged 65 Excretion urography disclosed a deep concavity and configuration of calyces in midportion of the kidney suggesting medial displacement of minor ramifications of lower infundibulum This proved to be a solitary cyst of the kidney Such a deformity is always to be differentiated from a solid type of tumor of renal parenchymal origin

Specimen (fig 2) consisted of a left kidney, with a large monolocular cyst at the inferior pole The kidney measured 12 by 6 by 3½ cm and weighed approximately 175 gm The cyst at the inferior pole was approximately 7 cm in diameter The capsule stripped readily, revealing a smooth red brown surface with a moderate degree of fetal lobulation The cortex was about 6 mm in width, with poor demarcation, and appeared blurred The medulla was not remarkable The cyst was thin walled and had a smooth, glistening, transparent lining The pelvis was granular and hyperemic Microscopic diagnosis Solitary cyst of kidney, mild pyelitis

Case 2 W S (105680) was a white man The right kidney (fig 3) measured 21 by 14 by 8 cm and was composed of several cysts The largest was 14 cm in diameter and extended from the superior pole A slightly smaller cyst was dependent from the inferior pole. There were several smaller cysts over the surface of the kidney. The portion identifiable as renal parenchyma measured 12 by 6 by 2 cm. The capsule stripped with slight difficulty, revealing a coarsely granular, pale pink-tan surface, with several shallow depressed linear scars. On sagittal section the cortex was of average width in most areas, except at one pole it was thinned to 6 cm. by pressure of adjacent cyst. Elsewhere the markings were somewhat blurred; the color was pale pink-tan. Corticomedullary junctions

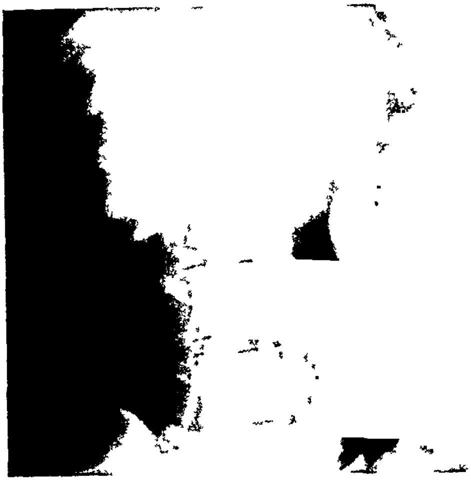

FIG. 1

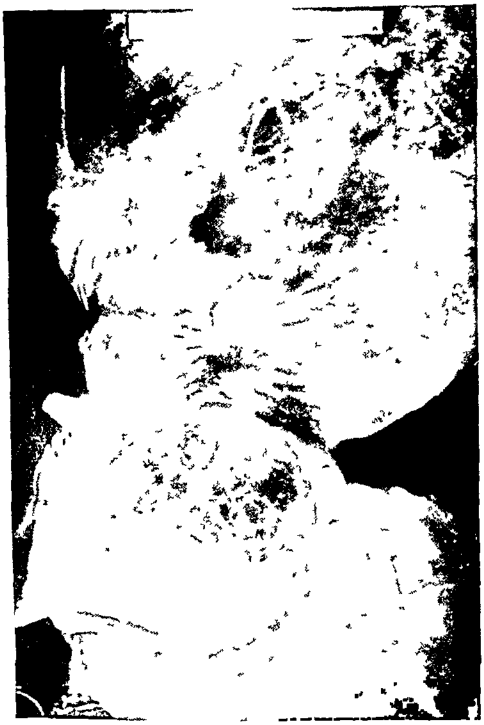

FIG. 2

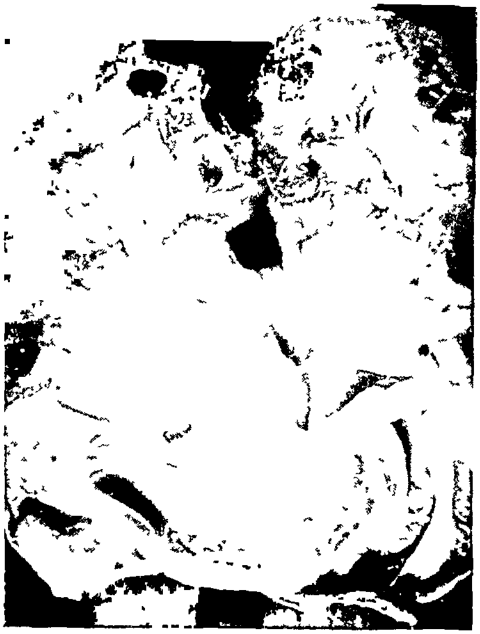

FIG. 3

were fairly well demarcated. The mucosa of the pelvis and ureters was delicate and smooth throughout, but the calyces and pelves were somewhat dilated. All the aforementioned cysts were lined by smooth pale gray linings and contained clear, slightly yellow fluid. The right ureter was slightly dilated, but the left was unremarkable.

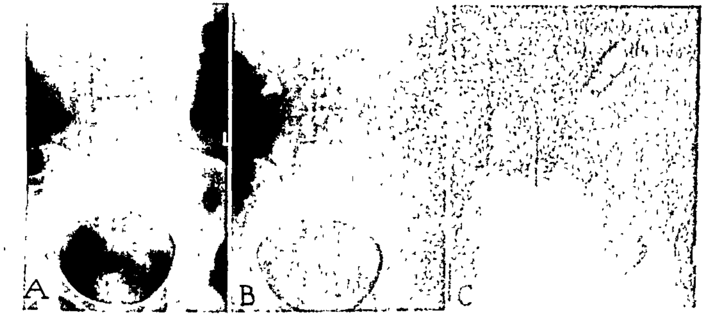

FIG. 4

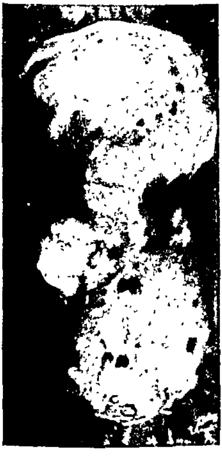

FIG. 5

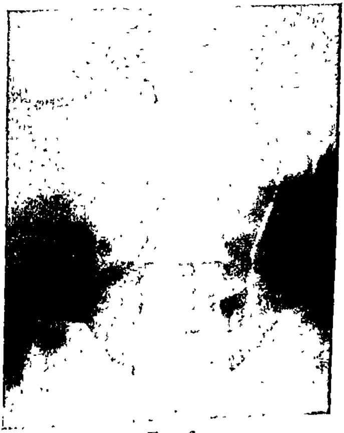

FIG. 6

Case 3. Mrs. D. N. (17405) was a white woman aged 49. A plain x-ray (fig. 4, *A* and *B*) revealed bulbous enlargement of the lower half of the left kidney shadow delineated by small arrows with a 4 mm. sized area of calcification near the hilum of this kidney as it was then located. Contrast study by excretion urography revealed upward displacement and flattening with linear broadening of the inferior calyx and the entire pelvic portion of the kidney with upper pole somewhat higher than usually seen. The calcification was situated in the medial portion of the inferior minor calyx which was described as displaced.

An evacuation film (fig. 4, *C*) after barium enema showed lateral displacement of the descending portion of the colon below the splenic flexure about the bulbous enlargement of the lower pole of the left kidney.

The bulbous enlargement and displacement of calyces, as described in the left kidney, were consistent with solitary cyst of lower pole of the kidney with size of cyst sufficient to displace colon as shown.

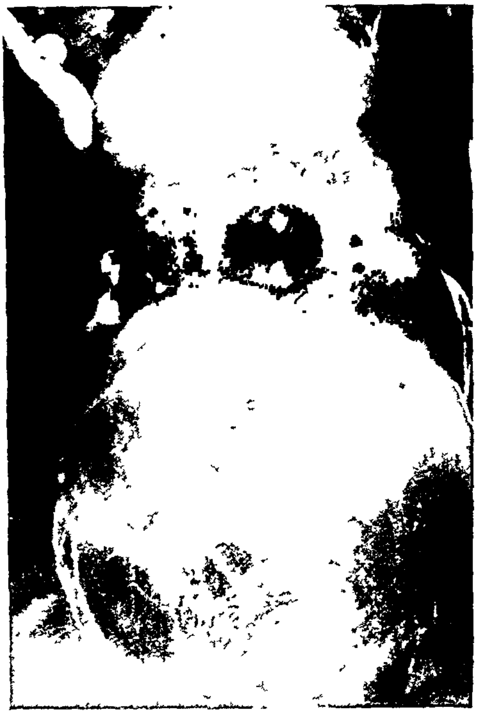

FIG. 7

Study of the gross specimen (fig. 5) showed multiple retention cysts and large unilocular simple cysts. The relationship of these cysts with polycystic disease is obscure; although most authors deny such relationship, we feel that such a relationship does exist.

Case 4. Mr. S. (120435). Excretory urography (fig. 6) showed rounded enlargement of lower pole of right kidney with upward displacement of renal pelvic structures and slight dilatation of renal pelvis major.

These findings were due to a large solitary cyst in lower pole of the right kidney with pressure on the upper portion of the ureter near the ureteropelvic junction, producing slight obstruction and resultant dilatation of the renal pelvis; the pelvic structures were displaced upward by the lower pole cyst. The gross specimen contained a massive retention cyst and multiple small retention cysts; also a large simple cyst of right kidney (fig. 7).

SUMMARY

The authors have herewith presented the many disconcerting problems concerning the subject of renal cystology. Embryologic origin has been thoroughly modernized in keeping with advanced embryologic knowledge and a clearer and more comprehensive classification has been suggested.

The authors are greatly indebted to Dr. Lester King, chief of pathology, Illinois Masonic Hospital, for his helpful assistance.

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55 E. Washington St., Chicago 2, Ill.

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CATHETERIZATION OF RENAL CYST FOR DIAGNOSTIC AND THERAPEUTIC PURPOSES

HARRY GRABSTALD

From the U. S. Public Health Service (Marine) Hospital, Norfolk, Va.

The purpose of this paper is to stress the value of renal cyst aspiration for diagnostic purposes. The first instance in which a cyst has actually been catheterized is presented; in this case the cyst appears to be of the multilocular variety and, if so, represents the first diagnosed in this manner.

In 1928 Colston described the first solitary renal cyst observed at the Brady Urological Institute. Dean in 1939 described aspiration of renal cysts in 15 patients. Symptomatic improvement was striking in many and functional improvement, by pyelography, was noted in one. In another, a previously resistant renal infection responded to subsequent chemotherapy. In the same year Fish presented 32 renal cysts with cure of two by aspiration and instillation of 50 per cent dextrose. The majority of cysts in this, as in other series, were of the lower pole variety and therefore easier to aspirate.

Recently, Ainsworth and Vest have re-introduced this technique and have described 9 cases in which this method was of distinct diagnostic aid.

Nelson, in discussing the paper of Smith, Rush and Evans, describes having observed a Swedish radiologist, Dr. Lindblom, utilize fluoroscopy in a modification of this renal cyst aspiration technique.

The significance of this diagnostic method in the differential diagnosis of renal cyst and tumor is manifest when we realize the impossibility of distinguishing these two disease entities by the usual x-ray techniques (Ochsner).

CASE REPORT

W. H. F., hospital No. 108205, a 67-year old white man was admitted without symptoms on August 18, 1952. Three months previously pyelograms were made elsewhere for purposes of investigating hypertensive disease. He was advised to have repeat examination for what appeared to be either a left renal cyst or tumor.

Examination: Blood pressure 179/110. There was moderate cardiac enlargement, a paradoxical pulse and a systolic aortic murmur.

Retrograde pyelograms revealed a space-occupying lesion of the lower pole of the left kidney (fig. 1, *A*). Perirenal air injection by the paracoccygeal route was successful, but of no further aid in differentiating renal cyst from tumor (fig. 1, *B*).

Utilizing the technique described by Ainsworth and Vest, a No. 15 gauge needle was inserted into the cyst without difficulty. A polyethylene tube was threaded through into the cyst and the needle removed. Fifty cubic centimeters of clear fluid was removed and submitted for cytologic study. Tumor cells were not observed. Fifty cubic centimeters of opaque medium were then instilled and

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films made. Figure 1, *C* represents a smooth lower pole cyst. Fluid was then aspirated and the cyst filled to half capacity and an upright film made. There was definite pooling of dye inferiorly with enough clinging to the margins of the superior cyst wall to suggest a multilocular cyst (fig. 1, *D*). Medium was again aspirated and air films made. A smooth wall was observed (fig. 1, *E*) with nothing to suggest a filling defect.

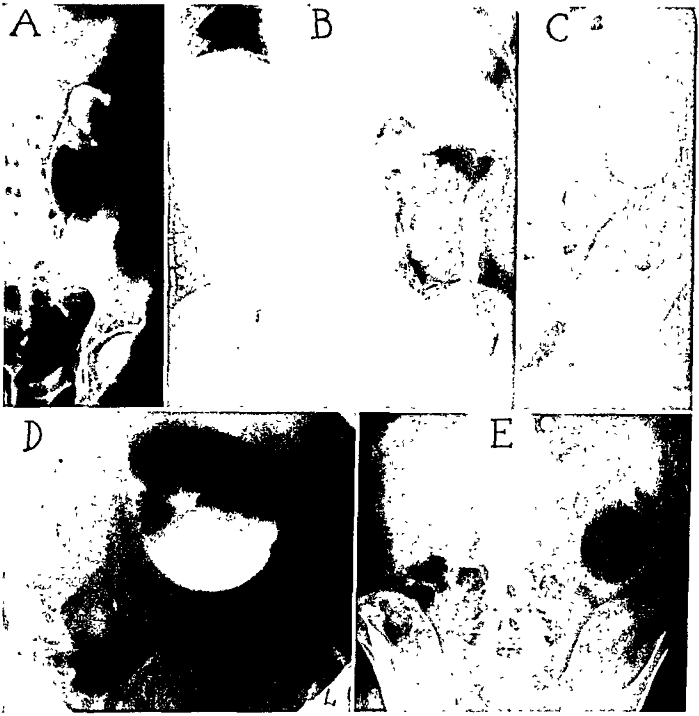

FIG. 1. *A*, retrograde pyelogram showing space-occupying lesion of lower pole; cyst or tumor. *B*, perirenal air injection (paracoccygeal route). *C*, opaque "renal cystogram." Non-opaque catheter not visualized. *D*, cyst filled to half capacity with patient in upright position. Multilocular nature of cyst observed. *E*, air "renal cystogram" showing absence of filling defect.

On subsequent days 50 per cent glucose was instilled into the catheter for purposes of attempted sclerosis. Blood sugar remained normal with the tubing clamped. It is doubtful, however, that enough glucose was instilled to accurately measure reabsorption. Indigo carmine injected intravenously did not appear from the tubing after several hours. Repeat retrograde pyelograms on the fifth day revealed no change in configuration of the previous deformity. The tube remained within the cyst for five days without causing untoward subjective or objective findings of any type. Penicillin was inserted into the cyst and the tubing removed. The patient was discharged without symptoms.

DISCUSSION

The obvious advantage of this technique in this case is that we have avoided major renal surgery in an elderly poor-risk patient. Another important advantage of this technique arises when one considers using aortography to differentiate tumor from cyst. Aortography is more difficult, dangerous, time-consuming and technical. The patient must be hospitalized and when the translumbar technique is utilized, general anesthesia is usually required. The technique described by Ainsworth and Vest is simple and is an office procedure.

A third conceivable advantage concerns the possible utilization of this technique to study the mechanism of formation, function and the reabsorptive capacity of renal cysts of various types.

Attempts to sclerose the cyst in our subject have failed. It is likely that the multilocular nature of the cyst was responsible. The therapeutic value in uncomplicated solitary renal cysts, however, has been proved by Dean.

Several disadvantages, theoretic and real, have been described and should be briefly discussed. Several extreme views have been expressed relative to aspiration of renal tumors. Fish believes the danger of spreading tumor (or producing infection incidentally) is negligible. Dean described "no harm" in aspirating 150 renal tumors. Recently Weyrauch, Wanless, Goebel and Scott have described their technique for formal renal biopsy in suspected tumors. They conclude that the "kidney may be incised safely without danger of spreading tumor cells." It would therefore appear that aspiration is even less likely to seed tumor cells.

Other investigators feel differently. Prather believes that "needle puncture should be reserved for the rare case in which surgery is indicated". The possibility of introducing infection or of starting hemorrhage is to be considered.

There is a possibility of missing a rare intracystic tumor. Wheeler describes missing an hypernephric cyst by this technique. Because of persistence of pain after renal cyst aspiration, his patient was operated upon and an adenocarcinoma in the cyst wall and adjacent kidney was found. The use of contrast air and opaque films should prevent such experiences.

SUMMARY AND CONCLUSIONS

The procedure of aspirating renal cysts described by Dean, Fish and Wheeler and recently re-introduced and modified by Ainsworth and Vest has been discussed. We have modified the procedure by introducing and leaving a polyethylene tube within the cyst for diagnostic and therapeutic purposes. What appears to be a multilocular renal cyst has been diagnosed in an elderly poor-risk patient, thereby avoiding surgery. If this is a multilocular cyst, it represents the thirty-second case described in the literature (Frazier) and the only one diagnosed without surgical intervention. Attempts at sclerosis of the cyst wall failed. There appears to be no definite untoward effects from this procedure described to date. The technique is simple and useful.

The author is indebted to Dr. Charles J. Cherre, chief of the Radiology Service for helpful suggestions.

Crile Veterans Administration Hospital, Cleveland, Ohio

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RENAL DISPLACEMENT AND PYELOGRAPHIC DEFORMITY PRODUCED BY AMEBIC INFECTION OF THE LIVER

DAVID GIVNER

From the Medical Service Veterans Administration Hospital, Fort Benjamin Harrison, Indianapolis, Ind.

Pyelographic deformity due to extrarenal disease is rare. A case of pyelographic deformity produced by an hepatic abscess has recently been described by Coppridge et al. for the first time.[1]

In this case, in addition to pyelographic deformity, there was a displacement of the right kidney and the right psoas muscle shadow was completely obliterated. The diagnosis of perinephric abscess was seriously considered. In so far as the presence of amebic liver abscess was thought to be most likely, the patient was given emetine therapy, which resulted in prompt improvement with subsequent restoration of the right kidney displacement and pyelographic deformity to normal. In view of the single case report and noteworthy differences stated above, it is felt this case merits addition to the literature.

CASE REPORT

R. M., a 32 year old white man, was admitted on April 13, 1949, to the Medical Service, Veterans Administration Hospital, Fort Benjamin Harrison, Indianapolis, Indiana, with the chief complaints of weight loss, right abdominal pain intermittently, and weakness since October 1948, fever and extreme weakness for 6 to 7 weeks prior to admission.

The patient stated he had pneumonia in the spring of 1948 from which he had an uneventful recovery with penicillin therapy. Following another attack of pneumonia in 1948, he continued to cough intermittently, became progressively weaker, and his weight decreased from 158 to 128 pounds. He experienced right abdominal pain from time to time, which was aggravated by coughing. Six to seven weeks prior to admission he became completely bedridden, had a continuous frontal headache and attacks of chills and fever. Six weeks prior to admission to our hospital, he was hospitalized elsewhere for several days. Following x-rays of his abdomen, he was told his right kidney had "fallen down." While stationed in the Philippines in World War II, he had attacks of diarrhea which the patient stated was common with his fellow soldiers. Examination of stools was made but the patient was not aware of the reuslts. He was not treated with any amebacides.

On physical examination, patient was found to be a chronically ill, white male, who appeared extremely pale and weak. Weight 124½ pounds, temperature 100F, pulse 80 per minute, blood pressure 118/68. Abnormal findings were essentially limited to the abdomen. Over the entire right abdomen, especially the right

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[1] Coppridge, W. H., Roberts, L. C. and Culp, D. A.: Pyelographic deformity produced by an hepatic abscess. J.A.M.A., **146:** 107, 1951.

upper quadrant, the right flank and the right costovertebral angle, there was tenderness to pressure. There was 3 plus spasticity over the right abdomen and right region posteriorly and laterally. The liver edge was not definitely palpable The spleen and kidneys were not palpable.

Initial blood count revealed 3,440,000 red blood cells, 10 5 gm. hemoglobin, 9,500 white blood cells, neutrophils 68 *per cent*, *bands* 2 *per cent*, *lymphocytes* 26 per cent, eosinophils 1 per cent, monocytes 3 per cent. Urinalysis revealed 2–4 white blood cells present per high power field. Serologic tests for syphilis were negative. Sedimentation rate 38 mm. per hour. Total protein 6 6 gm per 100 cc, albumin 4.0 gm. per 100 cc, globulin 2.6 gm. per 100 cc. Stool examinations were negative for parasites, including ameba. PSP test was within normal limits. Cephalin flocculation and thymol turbidity were negative. Initial chest x-ray revealed questionable elevation of the right diaphragm. Flat film of the abdomen revealed depression and obliteration of the right psoas muscle. The left retrograde pyelogram was normal. The right pyelogram showed depression, rotation, some displacement of the kidney to the midline with deformity and feathery appearances of the calyces (fig. 1, *A*). The gallbladder was not visualized on cholecystographic studies. Upper gastro-intestinal series was normal. During the course of the latter study some restriction in movement of the right diaphragm was noted. Barium enema revealed no evidence of any lesion of the large bowel or terminal ileum.

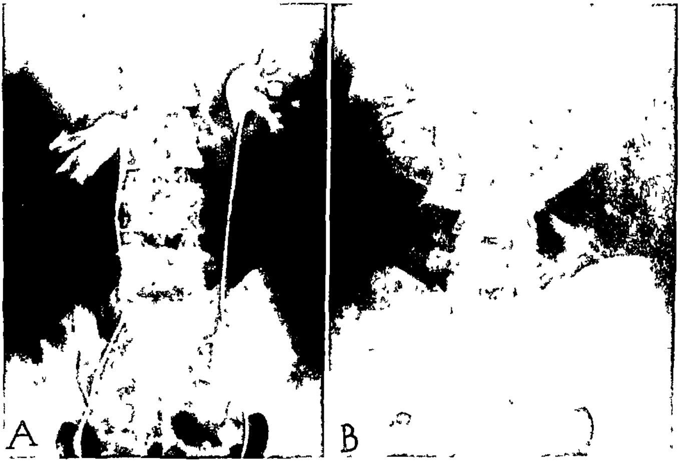

FIG. 1 *A*, bilateral retrograde pyelogram showing depression, rotation, displacement of right kidney to midline with deformity and feathery appearance of calyces. *B*, normal right retrograde pyelogram following treatment for amebic infection of liver. Abnormalities present prior to therapy are absent. Some barium present from gastro intestinal study.

On admission, the tentative diagnosis was hepatic abscess and right perinephric abscess. Five days after admission, the liver edge was palpable two fingers breadth below the right costal margin. Perirenal aspiration was negative. He continued to have a daily fever of 100 to 101. It was felt, if patient did not improve following emetine therapy, that an exploratory laparotomy should be performed. Emetine therapy was instituted 32 mg., t.i.d. for 10 days. Five days later, he was started on diodoquin .8 gm., t.i.d. for 10 days. Forty-eight hours after receiving emetine therapy he became afebrile, appetite improved greatly, abnormal physical findings over the right side of the abdomen, the right flank and the right costovertebral angle diminished considerably. Stool examinations continued negative for parasites. Another course of diodoquin therapy was started, 20 days after the first course was completed. His general condition had improved to such an extent that he was given a leave of absence. He returned to the hospital six days later, stating that pain had developed in the right upper abdomen, accompanied by chills, fever and nausea. His temperature was 101.6F, pulse 112 per minute, and there was 3 plus percussion tenderness over the liver, but the liver edge was not definitely palpable. He was started on another course of emetine therapy. Thirty-six hours later, his temperature was normal, and abnormal physical findings were practically nil. He continued afebrile and asymptomatic. His blood count returned to normal. A sample of blood which was submitted to the Army Medical Center, Washington, D. C., on May 23, 1949, was reported as showing a 3 plus complement-fixation test for amebiasis. A follow-up chest x-ray, another gallbladder series, and a right retrograde pyelogram (fig. 1, *B*) during convalescence revealed no abnormalities. Prior to discharge, patient stated he felt he could do a full day's work for the first time since October 1948.

COMMENT

A 27 year old white man, presented symptoms and findings compatible with the diagnosis of perinephric abscess or amebic infection of the liver. A flat film of the abdomen and pyelographic studies pointed to intrinsic or extrinsic renal disease. Liver became progressively larger. Following emetine and diodoquin therapy, patient became well. Pyelographic studies made during convalescence failed to reveal any abnormalities noted in the right kidney prior to therapy. In all probability, the abnormalities noted in the right kidney were caused by an amebic abscess of the liver rather than amebic hepatitis. However, the patient responded to medical therapy and exploratory laparotomy was not necessary. This case may bear out Klatskin's contention that amebic abscess of the liver can be cured completely by emetine without aspiration or surgical intervention.[2] Amebic infection of the liver should be considered in the differential diagnoses of displacement and pyelographic deformities of the right kidney.

[2] Klatskin, G.: Amebiasis of the liver, classification, diagnosis, treatment. Ann. Int. Med., **25**: 601-631, 1946.

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PROTRACTED URINARY TRACT SYMPTOMS DUE TO PARAMETRIAL CYST

JOSEPH A. LAZARUS

Mrs. L. P., aged 54, a childless housewife, first consultation March 25, 1938, complained of pain in the right loin, increased diurnal and nocturnal urinary frequency, burning on urination and occasional urgency, over a period of 3 months.

During the previous 7 years she had been treated for repeated attacks of right pyelitis. Fourteen years previously both tubes and left ovary were removed because of "inflammation."

She suffered attacks of fever and chills for 7 years and right loin pain. She had been subjected to many cystoscopic examinations and treatments. For the past 3 months she had been obliged to void every hour or two during the day and once or twice at night. Urination during this time was painful, and urine at times was sanguinous. Pain in the right loin was aggravated and occasionally the patient had severe colic with pain radiating from loin to groin. Owing to prolonged siege of illness, she became extremely nervous, irritable and lost considerable weight.

A complete urologic examination disclosed moderate degree of ptosis of the right kidney (with acute angulation of the ureteropelvic juncture) and slight right costovertebral tenderness, but was otherwise negative.

Physical examination, save for right costovertebral tenderness and a palpable right kidney, showed no abnormalities.

On May 6, 1938 an Albarran right nephropexy and ureterolysis was accomplished. Following an uneventful convalescence she was discharged from the hospital on the thirteenth day after operation.

The patient returned for examination May 17, 1942, approximately 4 years after nephropexy, stating that she again experienced pain in the right loin with increased urinary frequency and dysuria. A urologic examination now showed the kidneys in good position. Specimens of urine from the bladder and both kidneys were negative and the cultures sterile. Blood chemistry showed normal figures.

On physical examination a systolic apical murmur was found with moderate enlargement of the heart to the left. Blood pressure reading was 140/90 as compared to 120/80 at the time of the first examination. Right costovertebral tenderness was still present. Vaginal and rectal examinations were negative. Ureteropyelographic studies, excretory and retrograde, disclosed no abnormalities.

On April 30, 1943 the patient returned still complaining of pain in the right loin, increased urinary frequency and attacks which simulated biliary colic.

Physical examination was essentially similar to that of the previous year, except that now the liver edge was felt two fingers' breadth below the costal arch, and tenderness was elicited over the gallbladder. A Graham-Cole examination showed a poorly visualized gallbladder shadow with suggestive mottling

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On the assumption that the pain in the loin was in some way related to a diseased gallbladder, an abdominal exploration and cholecystectomy were carried out on May 6, 1943. The gallbladder was found thickened and presented pericholecystic adhesions, but there were no stones. No other abnormal condition was discovered in the abdomen. Following a normal convalescence the patient was discharged from the hospital on the fourteenth postsurgical day.

The patient was not seen during the next 5 years. On November 18, 1948, she returned complaining of pain in the right flank, without increase in urinary frequency or dysuria. A thorough urologic examination again showed no abnormalities except in the blood chemistry figures which disclosed an elevation of urea nitrogen and reduction of urea clearance and phenolsulfonphthalein. Careful pelvic and rectal examinations were negative.

BLOOD CHEMISTRY	MAY 20, 1942	NOV. 19, 1948
Creatinine	1.0 mg./100 cc	1.85 mg./100 cc
Urea nitrogen	12.0 mg./100 cc	16.9 mg./100 cc
Uric acid	2.6 mg./100 cc	1.3 mg./100 cc
Urea clearance ..	100.2%	68.0%

TWO HOUR PSP	MAY 20, 1942	NOV. 19, 1948
Total	59%	45.5%

Because of the persistence of pain in the right hypogastrium and loin, and history of postprandial belching, a complete study of the gastro-intestinal tract was carried out, with negative results.

On July 14, 1950 the patient returned and stated that following a course of aureomycin she had complete relief of symptoms for 5 months, after which the pain in the right loin radiating to the groin recurred. Two weeks previously she noticed that her urine was apparently purulent; there was greatly increased urinary frequency and dysuria. These signs and symptoms persisted for 10 hours. There was no fever. Urinalysis and right retrograde pyelogram were negative. Culture of urine was sterile.

One month later the patient returned, stating that she awakened during the previous night with an attack of increased urinary frequency and "burning." The urine appeared turbid. These symptoms and signs persisted for 2 days. She was well for 1 week, when she was again awakened during the night, but this time with a severe pain in the right loin. Urination was again frequent and painful. There has been no abatement of symptoms.

A right ureteropyelogram showed an acute angulation in the upper third and a moderate degree of ectasia of the middle third, of the ureter, and a second angulation opposite the sacral wing. The urine obtained from the kidney contained an occasional leukocyte, and was loaded with erythrocytes. E. coli was recovered from the bladder and right kidney urine.

In view of the normal pyelogram it was assumed that there was a small diverticulum of the lower end of the ureter which may have been previously overlooked because of possible closure of its neck Repeated ureterograms, however, failed to confirm this suspicion The patient by now had reached a stage where she insisted that something radical be done to relieve her suffering which had become unbearable Since it had been established that the left kidney was functionally efficient in maintaining life, it was decided to perform a careful exploration of the right kidney and entire ureter, and that if nothing definite could be found to account for the symptoms, a complete nephro-ureterectomy was to be carried out

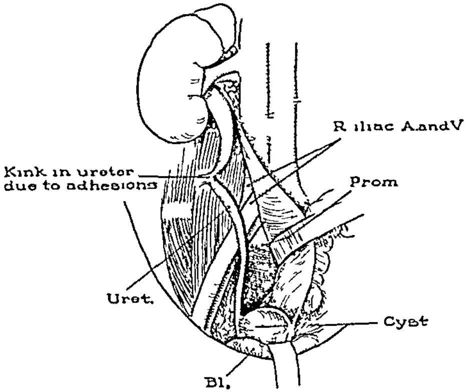

Fig 1 Schematic drawing showing relationship of retroperitoneal cyst to bladder and lower ureter and posterior parietal peritoneum

Operation (November 21, 1950) The kidney, which was exposed through an eight inch right Albarran incision through the previous scar, was found firmly adherent to the structures of the renal fossa and diaphragm, making it impossible to mobilize it along with its capsule A subcapsular renal exposure was therefore carried out and on careful inspection no abnormalities were found in the kidney itself The ureter, which was small, showed a thickened wall and acute kink at the junction between the upper and middle third caused by adhesions anchoring it to the quadratus lumborum After mobilizing the ureter down into the pelvis, no diverticulum was found A typical subcapsular nephrectomy was effected, including a part of the upper ureter

Following closure of the lumbar wound over appropriate drainage, the remaining part of the ureter was exposed extraperitoneally through a six inch Gibson incision In tracing the ureter down to the bladder, a cystic tumor was seen deep in the pelvis contiguous with the juxtavesical part of the ureter, and attached to the vesical wall adjacent to the ureteral area It was assumed, at first, that the tumor was intraperitoneal and probably an ovarian cyst After careful exposure the cyst was found to approximate the size of a tangerine and presented two flattened whitish plaques on its uppermost surface, to some extent resembling ovarian tissue Because of the assumption that it was an ovarian cyst, the peritoneum was widely opened and the abdomen and pelvis thoroughly explored, but no tumor was found. Re-examination of the growth showed it to be retroperitoneal and attached to the posterior parietal peritoneum by dense adhesions. See figure 1.

After tracing the ureter to the bladder, the tumor was completely mobilized from its bed by blunt dissection and removed. Following this the ureter was doubly ligated at its attachment to the bladder where it was severed with a carbolized knife. A rubber dam and tube were placed into the depth of the wound which was closed in layers.

Following a completely uneventful convalescence the patient was discharged December 4, 1950. There has been no recurrence of symptoms to date.

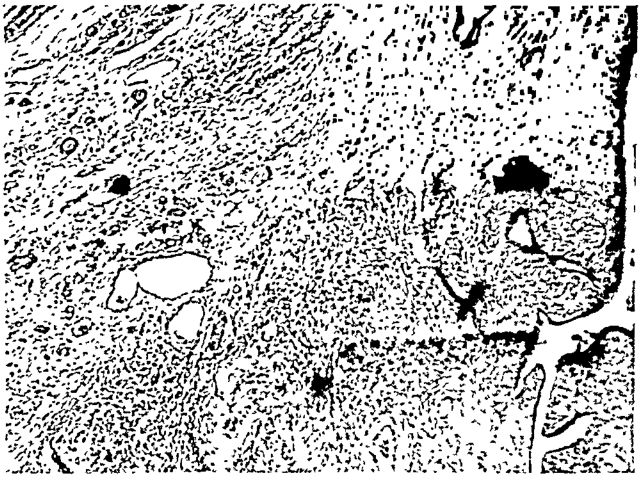

FIG. 2. Showing densely fibrous cyst wall and glands and some cysts. A few small cysts show rudimentary papillomatous excrescences.

The gross specimen consisted of a well-encapsulated cyst measuring 8.5 by 7 by 7 cm., the size of a peach. The lumen contained pale, water-clear, thin fluid. The internal lining was smooth. In places it was corrugated and contained ridges which gave a multiloculated aspect. The external well-encapsulated surface was smooth and in some sites rough. In one area there was a dime-sized plaque which was well encapsulated and adherent to the external surface. It measured 0.5 cm. to 1 cm. in thickness, and consisted of firm, fibrotic tissue of cartilagenous consistency.

Microscopic: The wall of the large cyst was lined by a single layer of flattened cuboidal cells with regular basally situated nuclei and peripheral pale cytoplasm. The wall was densely fibrous and in various areas contained small glands, cystic glands and cysts, lined by regular columnar cells with regular nuclei. These were more numerous at site of solid plaque noted on external surface of cyst. The latter plaque consisted of densely fibrous stroma which, in areas, had rudimentary papillomatous cysts lined by regular cuboidal cells. Diagnosis: The presumptive diagnoses were a) well-encapsulated benign serous cyst; b) encapsulated plaque of fibrocystadenomatous tissue forms part of the outer wall at one site; c) the tissue is probably of ovarian origin. See figure 2.

COMMENT

The most common extrinsic conditions inducing urinary tract symptoms in women may perhaps be classified succinctly as arising in the a) uterus and adnexa, b) gastro intestinal tract, c) central nervous system, and d) endocrine glands

Uterus and adnexa Uterine fibroids, malpositions and adnexal involvement, such as neoplasms involving the ovaries or tubes, not infrequently cause urinary tract symptoms These may be occasioned by irritation of the bladder wall through spreading infection from an adjacent salpingitis or from reduced vesical capacity caused by compression from an adjacent uterine or ovarian tumor Admittedly, many patients with uterine or adnexal abnormalities have no urinary tract symptoms Before concluding that an obvious extravesical pelvic lesion is solely responsible for urinary symptoms, it is advisable to make a careful urologic examination Only after excluding the urinary tract as the seat of pathologic changes, may one come to a decision that the symptoms are caused by disease of a woman's generative organs If the urinary tract is also found involved, the diagnosis is better withheld until the pathologic process in the urinary tract is eliminated as a causal factor

Gastro intestinal tract Urologists are well aware of the frequency of urinary symptoms resulting from pathologic changes in various parts of the intestinal tract It is common experience to find an anal fissure or a painful hemorrhoid causing increased urinary frequency, urgency, and at times, troublesome dysuria The most common lesions situated high in the colon likely to cause urinary tract symptoms are 1) cancer of the rectum, 2) cancer of the sigmoid adherent to the urinary bladder, 3) diverticulitis of the sigmoid adherent, or in juxtaposition, to the bladder, 4) pelvic abscess, usually of appendiceal origin, and 5) retrocolic appendicitis in close proximity to the ureter

Rectal cancer frequently induces symptoms referable to the urogenital tract, among which increased urinary frequency is probably the most common In patients with early lesions, urologic symptoms occasionally predominate to the exclusion of those referable to the rectum It is because of this that the urologist, in order to avoid making serious diagnostic errors, must make searching inquiries, particularly in regard to changes in bowel habit, and the passage of blood and mucus in the stools Because the majority of rectal cancers are situated low, they usually can be detected on careful digital examination I usually place the patient supine, with the knees flexed and drawn toward the chin The lubricated gloved finger is gently introduced into the rectum, the patient requested to strain, and the tip of the finger swung around the circumference of the rectal wall A sigmoidoscopic examination follows and biopsies are taken of any suggestive lesions

During the course of a cystoscopic examination a localized area of redness or bullous edema of the bladder wall may be found, usually on the posterior wall or vault This is suggestive of an extravesical lesion adherent to the bladder wall and warrants further studies to rule out one in the lower gastro intestinal tract

Cancers of the sigmoid may also cause urinary symptoms, especially when they are contiguous to the bladder. Careful interrogation of the patient regarding changes in bowel habit or stool characteristics may be indicative of serious pathologic bowel changes. Data thus obtained, regardless of their inconclusiveness, warrant a careful sigmoidoscopic examination followed by a contrast barium enema roentgenologic study.

Perhaps one of the most frequent lesions of the colon associated with urinary symptoms is diverticulitis of the sigmoid, because of the tendency of the affected loop to adhere to an adjacent viscus, especially to the urinary bladder. In well advanced conditions little difficulty should be found in localizing the seat of pathologic change because the symptoms are predominantly characteristic of some intestinal disorder. However, in patients with less advanced changes, vesical irritability often overshadows all other symptoms, and may lead to errors in diagnosis. Patients with acute diverticulitis are usually obese and give a history of longstanding constipation and pain usually confined to the left lower abdominal quadrant. During an acute episode, fever, leukocytosis and exquisite tenderness with possible rebound over the left lower rectus muscle, are usually present. The presence of a tender mass in the left iliac fossa is not unusual. Sigmoidoscopy supplemented by a barium enema roentgenographic examination may prove sufficient to establish the final diagnosis.

Pelvic abscesses are extremely prone to cause urinary symptoms. There should be little difficulty in making a correct diagnosis in acute conditions; however, when old, well-encapsulated abscesses are present there may be great bafflement. A careful digital rectal examination is obviously of great importance in recognizing this condition. Careful questioning may elicit a history suggestive of previous attacks of appendicitis. It is my confirmed opinion that patients who complain of urinary symptoms and reveal a pelvic mass on digital rectal examination should be given the advantage of an exploratory laparotomy.

Urinary tract symptoms may be present with retrocolic appendicitis because of the close proximity of the inflamed appendix to the ureter. In these examples the appendix is usually found acutely or subacutely inflamed with the inflammatory process spreading to the ureter and causing peri-ureteritis or ureteritis. Vesical irritability is probably caused by involvement of the ureteral nerve plexus by inflammatory reaction. In acute conditions percussion tenderness over the right loin can usually be elicited. An elevation of temperature and a number of leukocytes are often present. Passage of a ureteral catheter may disclose a narrowing or obstruction in the ureter where it comes in contact with the appendix. A specimen of urine obtained from the renal pelvis may show an absence of cellular elements, while urine obtained from the lower segment of ureter may show red or white blood cells or both. A roentgenogram taken after passing an opaque ureteral catheter to the right renal pelvis and after the administration of a barium enema may occasionally outline the appendix and its position in relation to the adjacent ureter. Appendicectomy is a justifiable procedure in doubtful conditions.

Neurogenic disturbances. Psychic or neurogenic disorders frequently lead to urinary tract symptoms, especially increased frequency. Although hysterical or neurotic women are prone to complain of bladder irritability, it must be remembered that these patients may, in reality, be suffering from organic changes in the nervous system Without entering into a detailed discussion concerning the various brain or spinal cord diseases that may cause urinary tract symptoms, a few of the more common conditions are tumor of the cord, usually situated in the area of the cauda equina, multiple sclerosis, as well as other varieties of degenerative lesions of the cord In fact, any disorder of the cerebrospinal system may occasion an atonic bladder, resultant from impaired innervation of the detrusor muscle with subsequent urinary incontinence or overflow The patient usually describes this as urinary frequency Reduced vesical capacity in those with contracted bladders resulting from hypertrophy of the vesical detrusor may occur in a variety of diseases of the central nervous system, and cause increased urinary frequency, urgency or strangury A urologic examination should always include cystometry as well as the standard neurologic tests, such as pupillary reflex, knee jerks, Romberg and Babinski tests, and an attempt to elicit evidence of saddle anesthesia

Increased urinary frequency often associated with tenesmus and dysuria may occur in women, who, as a result of some sexual disorder, find apparent relief in the practice of frequent emptying of the bladder Failure to recognize this underlying condition leads to failure in alleviating symptoms by customary therapy The urologist, usually consulted first, should be aware of the underlying maladjustment and confirm it by tactful interrogation The causes of urinary disturbance may be related to chronic passive congestion of the uterus and adnexa which affects the bladder by pressure and irritation, or it may be entirely attributable to psychogenic influence

Endocrine The relationship between the endocrine glands and water balance as it appertains to urogenital problems is a subject too complex for cursory discussion Suffice it to state that the pancreas, ovaries, pituitary and adrenal glands are the organs most frequently involved Diabetes mellitus, for example, gives rise to polydypsia, polyuria and increased urinary frequency, and errors in differential diagnosis should not be made

Diabetes insipidus, on the other hand, is frequently overlooked Here the fundamental defect is a failure of the normal physiologic control over the absorptive function of the epithelium of the convoluted tubules This control is the antidiuretic hormone elaborated by the pars nervosa of the posterior pituitary The polyuria is primary while the polydypsia is secondary and compensatory To avoid errors in diagnosing, the patient is requested to collect a specimen of urine in the morning after abstention from fluids following supper If the specific gravity is 1 006 or lower, the diagnosis is certain Diabetes insipidus can be ruled out if the specific gravity is 1 010 or over

In adrenal cortical insufficiency there occur a) increased loss of sodium and chlorides in the plasma owing to an increased loss of these ions in the urine, b) decreased output of potassium in the urine leading to a corresponding retention of this ion in the serum, c) elevation in the hematocrit occasioned by decreased plasma volume resulting from a loss of plasma fluids, d) increase in the plasma protein concentration; e) increased oxygen concentration of the blood, and f) impairment of renal function consequent upon decrease in the renal blood flow and followed by a rise in blood nitrogens. Urinary frequency results from impaired renal function.

SUMMARY AND CONCLUSIONS

The problem of urinary tract symptoms in women caused by extrinsic lesions is discussed. The causes are those pertaining to a) uterus and adnexa; b) gastro-intestinal tract; c) central nervous system, and d) endocrine glands.

An unusual case is described of longstanding urinary tract symptoms caused by a parametrial cyst, undetected on frequently repeated examinations, but which, during surgery, was found attached to the lower end of the ureter and bladder.

875 Park Ave., New York 21, N. Y.

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CYSTITIS EMPHYSEMATOSA: CASE REPORT

L. D. WHEELER

From the Department of Urology, Royal Prince Alfred Hospital, Sydney, Australia

Cystitis emphysematosa which is characterized by gas production in the bladder wall (usually due to bacterial activity) is an uncommon entity. The present report concerns its occurrence in a debilitated man with chronic retention of urine in whom the diagnosis was made by routine plain radiography of the urinary tract.

CASE REPORT

A man aged 66 was first seen on November 13, 1951 when he gave a history of increasing frequency of micturition and decreasing force in the urinary stream over the preceding 6 months. There had been no hematuria but there had been marked loss of weight over the period in question. He also had a cough which he attributed to pulmonary silicosis associated with his previous occupation as a coal miner.

He was a frail old man and on examination an insensitive distended bladder reaching above the umbilicus was found, with, per rectum, an adenomatous prostate with grade 1 rectal bulge. A provisional urological diagnosis of benign prostatic hypertrophy with chronic retention of urine was made. It was thought that the loss of weight was due to some non-urological cause, possibly gastric carcinoma.

No instrumentation was done at this stage nor had there been any instrumentation prior to his admission to hospital.

On November 14 urinalysis showed albumin 1 plus, sugar nil, with a few clumps of pus cells and occasional erythrocytes on microscopy. Culture returned B. coli. Hemoglobin was 9.5 gm. per cent, erythrocytes 3,340,000 and leukocytes 12,700 per cu. mm., with neutrophils 91 per cent, lymphocytes 6 per cent, monocytes 3 per cent. The blood Wassermann and Kline tests were negative.

X-ray of the chest showed dullness at the bases "partly due to fluid but there is some underlying lung pathology."

On November 16 a flat skiagram showed a markedly distended bladder whose wall was infiltrated with interstitial gas (fig. 1). A subsequent screening of the bladder with the patient erect showed a fluid level in the bladder.

At this stage cystitis emphysematosa was considered to be the probable explanation of the gas shadows and further urinalysis (November 20) showed small clumps of pus cells and 0–1 erythrocytes per high dry field. On aerobic culture a B. coli was grown in profuse amount and identified by the fermentations. No other organism was isolated in aerobic or anaerobic cultures.

On November 22 the first instrumentation took place in order to collect a sample of gas from the gas bubble in the bladder for analysis. The following technique was used. The patient voided and the urine was used to fill the lumen

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of a urethral catheter which now contained a column of fluid. The external end of the catheter was connected to a 3 way tap whose sidepiece was in turn connected to a tonometer. When the gas bubble had been tapped and gas was seen to flow out through the apparatus a sample was drawn into the tonometer vacuum. Analysis of the gas showed: CO_2, 6%; O_2, 4%; N_2, 90%.

After taking this sample the urethral catheter was withdrawn but acute retention of urine developed soon afterward and the patient was treated with an inlying urethral catheter, a mixed sulfonamide preparation by mouth (1 gm. thrice daily) and flavine bladder-washes.

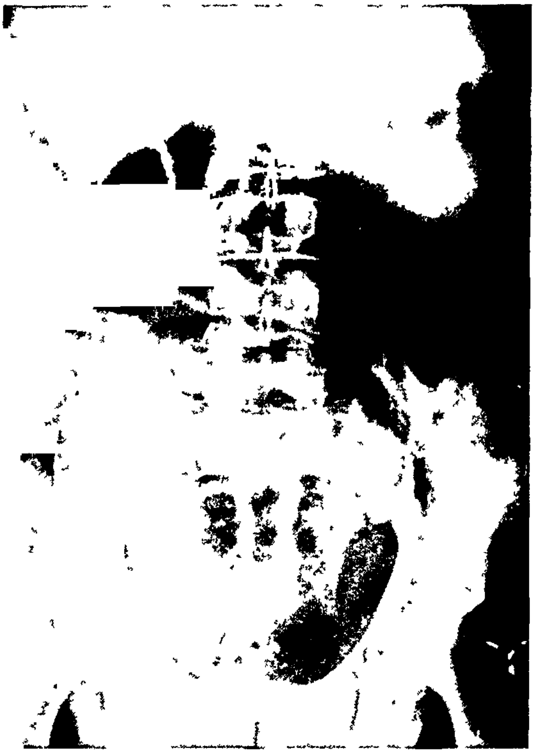

FIG 1

On November 26 cystoscopy was carried out under intravenous anesthesia. A moderate obstructing prostate was noted and the bladder wall showed marked coarse trabeculations. There was little evidence of cystitis and no hemorrhages, but multiple submucosal air vesicles were seen, varying in size up to approximately 0.75 cm., arranged singly or in clumps and rows. The appearance was very similar to that seen in the visceral pleura in cases of interstitial emphysema, or as Antoine[1] picturesquely states, like "a mercury-injection-preparation of lymphvessels" (ein Quecksilberinjektionspraparat von Lymphgefaben).

A further cystoscopy on November 29 (16 days after admission) showed that the lesions had almost completely disappeared, a few vesicles only remaining.

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[1] Antoine, T · Zur Klinik der Cystitis emphysematosa Zentralbl f Gynak , **38**: 2230–2235, 1934.

An excretory urogram showed a normal upper urinary tract and further chest radiography resulted in a diagnosis of primary carcinoma of the lung A cholecystogram and barium meal were negative

On December 12 the patient was transfused with 1 liter of blood so that on December 15 the hemoglobin value was 12 5 gm per cent

On December 17 a transurethral resection of the prostate was performed, the prostatic tissue showing benign hyperplasia only At the resection it was noted that the bladder wall was quite free of air vesicles On December 23 the residual urine measured ½ ounce and the patient subsequently had a satisfactory urinary function

On January 14, 1952 a glucose tolerance test was performed with the following normal results Before glucose, 29 mg per cent, ½ hour 141 mg per cent, 1 hour, 168 mg per cent, 1½ hours 121 mg per cent, 2 hours, 141 mg per cent There was no glycosuria at any time during the patient's hospitalization

The patient's temperature was 100F on admission and on the day after admission but apart from a rise to 101F the day following transurethral resection he was afebrile

On January 19 the patient was noted to have become very weak and breathless while at rest in bed and progressively lost weight and died on February 22, 1952, a little over 3 months after admission

Autopsy (Dr V J McGovern) showed a carcinoma arising from the bronchus supplying the left lower lobe and also numerous miliary tubercles in the lungs The kidneys were macroscopically normal The bladder contained a good deal of purulent urine and a fibrinopurulent exudate in the mucosa, beneath this, for the most part, the mucosa was injected and in places ulcerated The trabeculae in the posterior portion of the bladder were prominent The prostate "had been subjected to transurethral resection" Microscopically the lung showed an aplastic carcinoma and in addition miliary tuberculosis Nodules throughout the lungs and pleurae were acute tuberculous lesions The liver showed a small caseating tuberculous focus, the kidneys some focal interstitial nephritis, and the bladder a very mild inflammatory infiltration of the bladder submucosa, most of the surface epithelium having been shed The colon showed diverticulosis The autopsy diagnosis was 1) carcinoma of lung with metastases, 2) miliary tuberculosis, 3) benign hyperplasia of prostate, 4) cystitis, 5) diverticulosis coli

PREVIOUS CASES

According to Antoine,[1] cystitis emphysematosa was first described as a postmortem finding by Eisenlohr in 1888 and (if Lautenschlager's report of 1911 is excluded, diagnosis according to Ravich and Katzen[2] not having been certainly made antemortem) it was not until 1932 that the lesion was first diagnosed during life by Ravich and Katzen[2] at cystotomy Twelve other cases diagnosed during life have been reported since then These cases are summarized in table 1

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[2] Ravich, A and Katzen, P Cystitis emphysematosa Review of the literature with report of an authentic case terminating in recovery J A M A, 98 1256–1259, 1932

TABLE 1. *Reported cases diagnosed antemortem*

	REPORTED BY	DATE	SEX	AGE	PRESENTING SYMPTOMS	DIAGNOSED BY	CONFIRMED BY	ORGANISM	DIABETES MELLITUS	APPROXIMATE DURATION OF LESION (DAYS)	REMARKS
1	Ravich and Katzen[2]	1932	M	56	Hematuria	Cystotomy		Colon bacillus B. coli	No	17	Vesical diverticulum
2	Antoine[1]	1934	F	38	Hematuria	Cystoscopy	Pricking vesicles	Cl. welchii	No	10	Onset after difficult labor
3	Redewill[3]	1934	M	58	Hematuria	Cystoscopy	X-ray and collection of gas	B. coli	No	21	
4	Redewill[3]	1934	F	72	Chronic cystitis	Cystoscopy	Collection of gas	B. coli. Cl. welchii. B. hemolytic streptococcus	No	"Disappeared rapidly"	
5	Burrell[4]	1936	F	57	Hematuria	Cystoscopy		B. coli	D.M.	5-7	
6	Levin[5]	1938	F	57	Hematuria	Cystoscopy		Cl. welchii	D.M.	"Disappeared almost immediately"	Infection of L. hallux
7	Lund, Zingate and O'Dowd[6]	1939	M	71	Pneumaturia	X-ray	Cystoscopy	B. coli	D.M.	3	
8	Wilhelm[7]	1939	M	40	Pneumaturia and hematuria	X-ray	Cystoscopy	B. coli	D.M.	"Disappeared promptly"	Relapsed in 3 months. Cured again with sulphomamide
9	Marquardt[8]	1940	F	56	Dysuria	Cystoscopy		B. coli. Strept. faecalis	D.M.	4	
10	Burns[9]	1943	F	72	Frequency	Cystoscopy	X-ray	B coli. Cl. welchii. B. hemolytic streptococcus	No		Died 38th day
11	Ortmayer[10]	1948	F	64	Hematuria	Cystoscopy		B. coli	D.M.	4	R. infected hydronephrosis. R. nephrectomy
12	Teasley[11]	1949	F	65	Loin pain	X-ray	Cystoscopy	B. coli	D.M.		Died 4 weeks later
13	Maurer, Lich and Burdon[12]	1949	M	42	Hematuria	Cystoscopy	X-ray	B. coli	No	Disappeared rapidly	Peptic ulcer
14	Present case		M	66	Chronic retention	X-ray	Cystoscopy	B. coli	No	14	Obstructing Prostate. Carcinoma of lung

DISCUSSION

The problem of the relationship between cystitis emphysematosa and gas cysts of the intestine, colpitis emphysematosa and emphysematous cholecystitis is a facinating one

Gas cysts of the intestine occur commonly in pigs that have been fed a diet mainly consisting of polished rice and in humans in association with peptic ulcer where the diet may have a low protein value (King[13]) The etiology of colpitis emphysematosa is not explained (Bender and Jeffcoate[14]) nor is that of emphysematous cholecystitis (Friedman, Aurelius and Rigler[15])

The emphysematous bladder lesions may be associated either with Cl welchii which may (Redewell's[3] "Class 1") or may not (Antoine,[1] Levin[5]) be fatal, or more commonly are associated with coliform infection (coliforms do, of course, produce gas in a suitable substrate) and the patient may, or may not, be diabetic In the diabetic the urinary and tissue sugar is the obvious source of the gas but in the non diabetic patient the normal tissue sugar and/or tissue, or urinary protein or extravasated blood must be regarded as the substrate (Antoine[1])

The figure for the CO_2 (6 per cent) in the present case can only be explained by remembering that the gas in the bubble in the bladder approaches an equilibrium with normal tissue gases in solution

There was little, if any, generalized cystitis present in this patient so this present case would be regarded by Redewell[3] as a case of "cystitis pneumatosis cystica" or cystitis emphysematosa class 4

The course of the lesion itself in this case and in the other cases reported in the living is essentially benign and of short duration, hardly a "disease" per se

SUMMARY

A case of cystitis emphysematosa occurring in a debilitated non diabetic male aged 66 and associated with coliform infection is reported

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[3] Redewill, F H Cystitis cystica emphysematosa Urol & Cutan Rev 38 537–543, 1934

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[11] Teasley, G H Cystitis emphysematosa Case report with a review of the literature J Urol **62** 48 51, 1949

[12] Maurer, F E Lich, R and Burdon, S Cystitis emphysematosa a report of the fourteenth human case diagnosed at cystoscopy Urol & Cutan Rev, **53** 530–531, 1949

[13] King, E S J Gas cysts of the intestine Aus N Z J Surg, **20** 25 32 1950

[14] Bender, S and Jeffcoate, T N A Vaginitis emphysematosa J Obst Gynaec Brit Empire, **57**. 432–436 1950

[15] Friedman J, Aurelius, J R and Rigler L G Emphysematous cholecystitis Am J Roentgenol & Rad Therapy **62** 814 822, 1949

The diagnosis was made by a routine urinary tract skiagram which showed characteristic gas shadows in the bladder wall.

The lesion itself (in this as in most other reported cases) was transitory and benign.

My thanks are due to Dr. M. S. S. Earlam, Honorary Urologist, Royal Prince Alfred Hospital, Sydney for permission to publish this case report and to Professor F. S. Cotton, Professor of Physiology, the University of Sydney, for the gas analysis.

Royal Prince Alfred Hospital, Sydney, N.S.W. Australia

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POSTOPERATIVE URINARY INCONTINENCE, A REVISED CONCEPT OF THE EXTERNAL SPHINCTER[1]

JAMES S ELLIOT

From the Division of Urology, Department of Surgery, Stanford University School Of Medicine, San Francisco, Calif

This paper presents a revised concept of the external sphincter as an initial step in investigating the causes and rational correction of postoperative urinary incontinence See figures 1–6

In current concept, the striated musculature of the urethra lying within the triangular ligament is assumed to constitute the external urethral sphincter Injury to this muscle is commonly regarded as the factor responsible for the production of urinary incontinence The external sphincter is generally considered to be entirely voluntary, and inability to maintain continence is frequently ascribed to the patient's unwillingness to exert conscious effort to hold his urine

In contrast to the foregoing concept, there is good reason to believe and much evidence to show that urinary continence is primarily an unconscious or involuntary act dependent upon the efficient activity of the smooth muscle and connective tissue about the urethra, and that the striated muscle is only an accessory The basis for this revised concept is contained in observations on the nature of micturition in normal individuals, in those with disease of the spinal cord, on certain anatomic relationships of the male urethra, and on observations of patients who have undergone prostatectomy

The role of smooth muscle in maintaining continence is suggested by the involuntary aspects of micturition It is known that most individuals are unaware of their bladder until it contains about 250 cc of urine or in some instances, more During the period of filling no effort is needed to maintain continence Except when there is an extremely urgent desire to void, neither the normal individual nor the usual post-prostatectomy patient needs to consciously contract his perineal muscles to avoid losing urine Conscious effort is impossible during sleep Infants too young for voluntary control are yet not incontinent Some individuals with atrophy of all the striated muscles of the perineum due to injury to the spinal cord or cauda equina void reflexly without incontinence Much of the above has been demonstrated experimentally on live human subjects by Denny-Brown and Robertson In addition, they have shown that willed micturition and cessation of voiding depend primarily upon the reflex and reciprocal activity of the detrusor and urethral musculature Contraction of the striated urethral muscle is vigorous, but capable of only briefly sustained activity From their experiments, they concluded that it served as an accessory only and as such was analogous to the external anal sphincter, which has been shown by Gaston to be capable of vigorous voluntary contraction lasting only a few seconds

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[1] Read at annual meeting, Western Section, American Urological Association, Pasadena, Calif , May 21, 1952

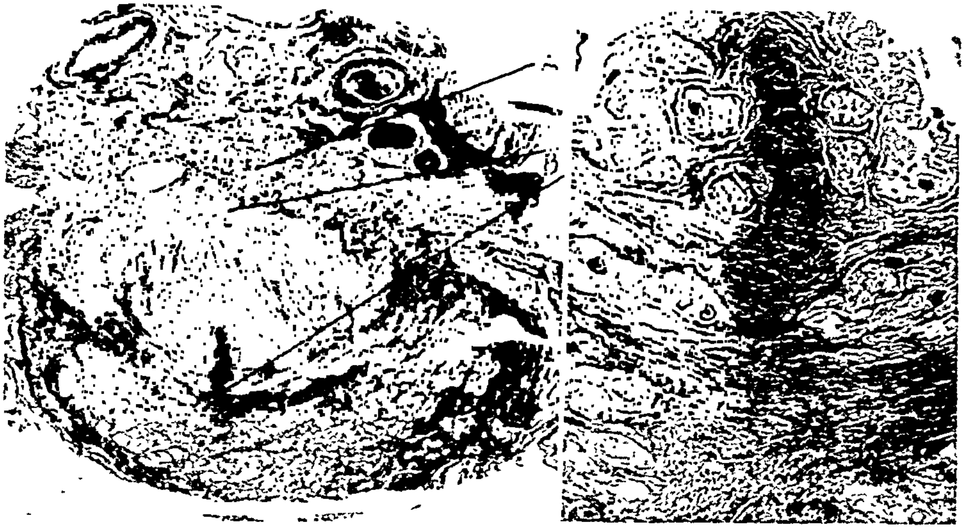

FIG. 1. Left, low power photomicrograph of prostatic apex in cross section showing location and extent of striated muscle (*A*), and smooth muscle and connective tissue (*B*). Right, higher power showing circular smooth muscle posterior to lumen of urethra.

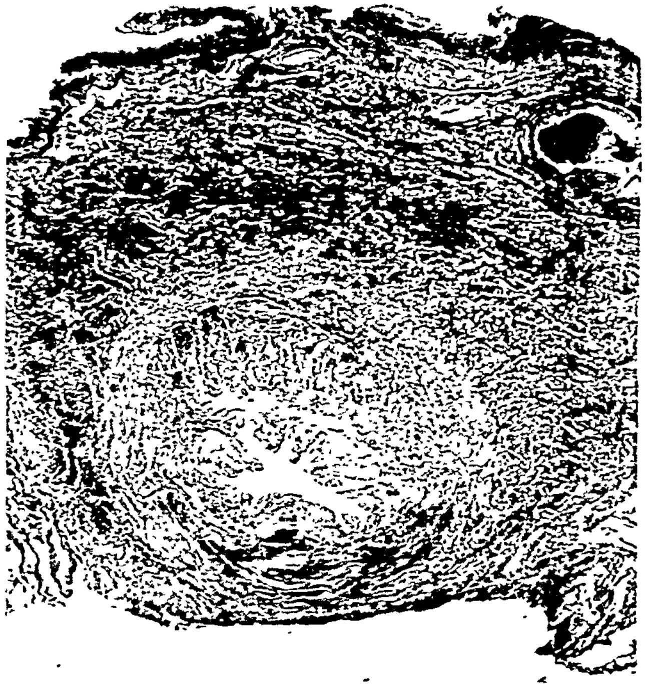

FIG. 2. Low power photomicrograph of membranous urethra showing striated muscle anteriorly and laterally, and external to smooth muscle and connective tissue ring about lumen of urethra.

In order to clarify the relationships of smooth and striated muscle about the urethra, reference was made to the detailed description by Kalischer, and the work of Wesson. In addition, sections of three post-mortem specimens of intact prostate and urethra were prepared with differential stains. The urethra is invested with circular and longitudinal coats of smooth muscle from the bladder neck to the anterior aspect of the triangular ligament. The prostate is a glandular structure which is inserted as it were into the smooth muscle distal to the bladder. Its stroma is made up in large part of smooth muscle. Between the bladder and prostate there is an increase in the number of fibers which encircle the urethra. Distal to the prostate there are again circular smooth muscle fibers. Examination of microscopic sections has shown that there is a considerable layer of smooth muscle between the mucosa and the striated muscle,

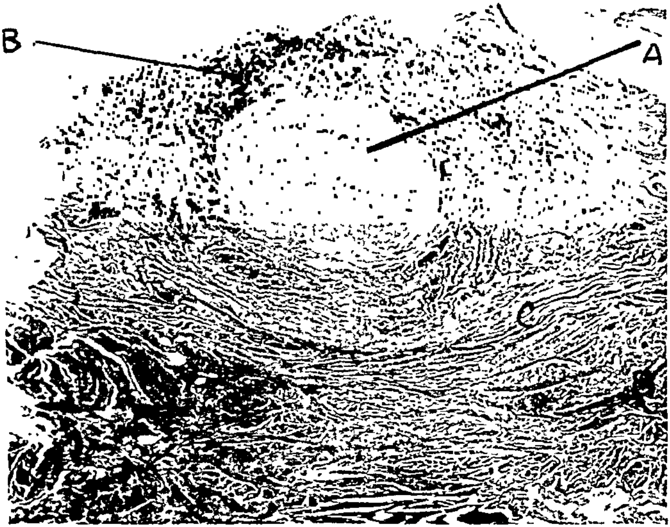

FIG. 3. Low power photomicrograph of triangular ligament showing ring of smooth muscle and connective tissue about urethra (*A*), striated muscle (*B*), smooth muscle running transversely posterior to urethra (*C*).

and that smooth muscle and connective tissue make up the bulk of the urethral wall. Anterior to the prostate, but within its capsule in the vicinity of the bladder neck, there are a few fibers of striated muscle. As the triangular ligament is approached these fibers become greater in number and extend farther and farther laterally, so that finally between the fascial layers of the triangular ligament they completely encircle the urethra to form the compressor urethrae. This layer of striated muscle lies on top of the urethra and outside its smooth muscle sheath like a cap. The urethra is almost completely encircled by striated muscle only as it traverses the triangular ligament. It should be emphasized that the posterior wall of the prostatic apex and membranous urethra is composed entirely of smooth muscle and connective tissue, which continue to invest the urethra to the distal aspect of the triangular ligament. Rolnick and Arnheim confirm its role as an accessory. The conclusion seems inescapable that postoperative incontinence is due to the excessive removal of smooth muscle and connective tissue in the vicinity of the prostatic apex and membranous urethra. This of course, is far more likely to occur than injury to the triangular ligament, in view of the distance between this structure and the verumontanum.

To recapitulate, urine is normally held at the bladder neck; after prostatectomy at the apex—in both cases as a largely unconscious function mediated by smooth muscle. There is physiological and anatomic evidence to show that the striated urethral muscle is only an accessory. Its loss does not cause incontinence in the presence of an intact proximal urethra. Its presence does not guarantee continence. Since urine is normally held in the vicinity of the prostatic apex following destruction of the bladder neck, and incontinence frequently follows its removal during total prostatectomy, loss of normal urethral tonus at this point due to the excessive removal of smooth muscle and connective tissue seems a logical explanation of the cause of postoperative urinary incontinence.

SURGICAL CORRECTION

Surgical correction of incontinence is most feasible in the female. Stress incontinence is sufficiently common and the urethra is so easily accessible, a wide variety of operative procedures have been attempted in efforts to restore normal urinary control. The types of operation which have been reported are summarized in table 1. It will be seen that three basic principles have been employed. The first, the Kelly or Kennedy procedures, consists of a plication of the bladder neck or bladder neck and urethra. The second consists of an attempt to utilize strips of striated muscle to compress the urethra. The third consists of the use of fascial strips to support or elevate the bladder neck or urethra—in effect affording external compression against the symphysis. The Marshall-Marchetti procedure is included in the last group since use is made of the vaginal wall to accomplish the same result. The common denominator in all these procedures is compression of the urethra, or narrowing of its lumen.

Surgical correction of incontinence in the male is less common, and there is no procedure which has been proved to be satisfactory. Several operations to remedy incontinence in the male have been described in the literature. Hugh Young reported 4 cases operated by a combined plication of membranous urethra and triangular ligament (preceded by excision of the posterior wall of the urethra) and wedge excision of a portion of the bladder neck transvesically with closure to reduce its calibre. He was apparently attempting to restore both internal sphincter and external sphincter. From his follow-up description of these patients, it seems clear that the plication of the membranous urethra accomplished nothing, and that troublesome strictures of the bladder neck resulted.

Vergés-Flaqué looped a portion of the striated external anal sphincter anterior to the bulbous urethra. Cooney and Horton passed strips of rectus fascia anterior to the symphysis and looped them below the bulb to produce a constriction at this point. Strong and Van Buskirk brought fascial strips from the rectus retropubically to form a fascial sling in the region of the membranous urethra. Hock has reported a similar procedure following total prostatectomy by the retropubic approach.

Keeping in mind the concept of the external sphincter as a composite of, primarily, smooth muscle and, only secondarily, striated muscle, a logical approach to surgical correction of postoperative incontinence would seem to consist of plication of the urethra in the vicinity of the prostatic apex with the aim of increasing the passive or unconscious urethral resistance in this area. According to this principle, 5 operations have been performed on 4 patients.

TABLE 1 *Operative procedures for incontinence in the female*

PLICATION PROCEDURES

Kelly operation 1914 Simple plication of the bladder neck
Kennedy operation 1937 Plication of bladder neck and urethra

MUSCLE TRANSPLANTS

* Goebel 1910 Pyramidalis muscle transplanted retropubically and under urethra
* Frangenheim 1917 Modification of above combining muscle and fascia
* Stoeckel 1917 Combined above with plication of vesical neck
* Giordano 1907 Transplanted gracilis muscle and wrapped it around urethra
* Squier 1911 Inserted portion of levator and muscles between urethra and vagina
* Martius 1929 Transplanted bulbocavernosus muscle between urethra and vagina

FASCIAL SLINGS

* Thompson 1923 Transplanted rectus muscle and fascia downward anterior to symphysis and under urethra
* Miller 1932 Used strips of fascia and pyramidalis muscle in same fashion
Aldridge 1942 Transplanted strips of rectus fascia behind symphysis and sutured them under urethra
Shaw 1949 Used fascia from thigh in form of sling under urethra passing ends through holes drilled in symphysis Also used tantalum gauze in same fashion
Marshall, Marchetti 1949 Sutured vagina and urethra to symphysis—using vaginal wall as a sling
Doolittle 1952 Same as above, but sutures placed through vagina only

* Data from Aldridge

Procedure 1 The prostate and membranous urethra were exposed perineally. The triangular ligament was divided in the midline. The membranous urethra from the distal aspect of the triangular ligament to the apex of the prostate was then plicated with mattress sutures of fine silk, so that a No. 14 catheter was snugly held. The triangular ligament was then plicated with heavy braided silk, and the wound simply closed. The catheter was removed on the tenth day. No improvement was noted following removal of the catheter. One patient was operated upon by this procedure, and 6 months later reoperated upon by procedure No. 2.

Procedure 2 The prostate and membranous urethra were exposed perineally. An elliptical portion of the posterior prostatic wall and proximal membranous urethra was then excised. Closure and plication of the membranous urethra and prostatic apex were then done with mattress sutures of 000 chromic. An attempt was made to secure a snug fit for a No. 12 catheter. The catheter was removed on the sixth day. Four patients were operated by this technique. Two were apparently cured for about eight weeks, but then, reverted to incontinence.

In addition to the foregoing, 1 patient was operated by the procedure suggested by Strong and Van Buskirk. This failed completely.

DISCUSSION

It might be well to consider the procedures in the male which are technically feasible. They are listed as follows:

1. *Plication of the triangular ligament and membranous urethra.* From the reports of Young, and the experience with one case reported here, this is unsatisfactory.
2. *Transvesical closure of the bladder neck.* In most of Young's cases troublesome strictures developed, although one case was apparently successful.
3. *Plication of prostatic apex.* Four cases of this type are reported in this paper. Although two were temporarily successful, all were utlimately failures.
4. *External compression of bulbous urethra by muscle or fascia.* Since there is normally no sphincteric action in this portion of the urethra, one could not expect a physiologic restoration of function.
5. *Compression of membranous urethra and apex by retropubic sling.* One successful result has been reported by Strong and Van Buskirk. Their success is analogous to results obtained from sling procedures reported by Hock following total prostatectomy, and in the female. One unsuccessful case is reported here.
6. *Retropubic wedge excision of prostate and bladder neck.* There are no reports in the literature of this having been done.

On the basis of analogy to the successful results following plication operations in the female, one might expect good results following simple posterior plication of the prostatic apex in the male. However, on the basis of my experience with this procedure, I am satisfied that this principle used alone will not result in consistent cures. The fact that two patients showed temporary improvement suggests that a modification of this procedure might be successful.

SUMMARY

A revised concept of the external urethral sphincter is presented, in which the sphincter is regarded as being composed essentially of smooth muscle, which acts primarily in a reflex or unconscious manner to maintain urinary continence. The striated urethral muscle functions as an accessory, and alone does not constitute the external sphincter.

The technical aspects of the surgical repair of urinary incontinence are reviewed and discussed. Six operated cases are presented.

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RESULTS OF SURGICAL TREATMENT OF 10 CASES OF MYOSARCOMA OF BLADDER

JEAN CIBERT and LOUIS DURAND

From the Clinique Urologique, Pavillon V, Hôpital Edouard Herriot, Lyon, France

From 1937 to 1950, out of an aggregate amount of 250 malignant tumors of bladder, we have observed 10 cases of myosarcoma (4 per cent). The purpose of our report is to make known the results obtained through the treatment of these cases.

1) Eight patients passed away; all had leiomyosarcoma.

Five patients had been treated by resection of the tumor after cystostomy. A 69 year old woman, affected by diabetes, died of it, 1 month after operation. Four others died of a relapse 1 month, 2 months, 4 months, 1 year, respectively, after the ablation, in spite of the relative benignity of the tumor (narrow pedicle and apparently normal vesical wall); in 3 of those operated upon, the relapse took place with surprising rapidity as if the operation had been the cause of an increase of malignity, filling up the bladder within few weeks, swelling it up, overgrowing externally through the cystostomy wound, and causing death through ureteral obstruction (uremia, pyelonephritis, cachexia).

One patient was treated by ureterosigmoidal implantation, since the bladder could not be removed. Death resulted through cachexia 1½ months afterwards.

One patient underwent total cystectomy at one sitting. He died of pelvic recurrence 13 months after the operation; nevertheless the tumor, small and pediculated, seemed to respect the vesical wall.

One patient, treated by transurethral resection, has been lost sight of, but most probably, he is dead.

2) Besides those 8 fatal issues, 2 results are worth while to publish: a more than 4 year cure of a leiomyosarcoma after total cystectomy in a single time; paradoxical cure of a nearly 7 year old myosarcoma after a simple transurethral resection.

Mrs. D., aged 58, was sent to Pavillon V on April 13, 1948 with a diagnosis of carcinoma of the bladder. The first symptom was a single episode of hematuria which happened 8 months previously, in August 1947. A little later on, dysuria appeared; at the early part of it, micturition was normal, but ended drop by drop, often leaving the impression that the act was incomplete; the frequency was little increased (only once at night). On March 26 the second episode of hematuria occurred. On the 28th, a urologist discovered, through cystoscopy, a widely pediculated round tumor on the posterior wall, and advised cystectomy.

Following cystoscopy, the symptoms became more serious; the dysuria became more intense and painful; the patient had to void every 2 hours. It was in that condition that the patient arrived at Pavillon V on April 13.

Introduction of a catheter was difficult; the urine recovered was very purulent.

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Vaginal investigation combined with abdominal palpation disclosed a mobile, firm mass of the volume of a tangerine but not infiltrating the bladder. It was easily seen in a cystogram (fig. 1); the kidneys were normal and the ureters undilated. The endoscopic aspect of the tumor was sphacelic; that is, that of leiomyosarcoma.

On April 28 a total cystectomy was performed. The vaginal stage was done first, with excision and ligature of the urethral meatus, dissection of urethra, retrosymphysary then vaginal release of the bladder; the urethra was put back into the pelvis. The abdominal stage was done next. The fore part of the bladder and peritoneum was widely freed from the back face of the recti muscles.

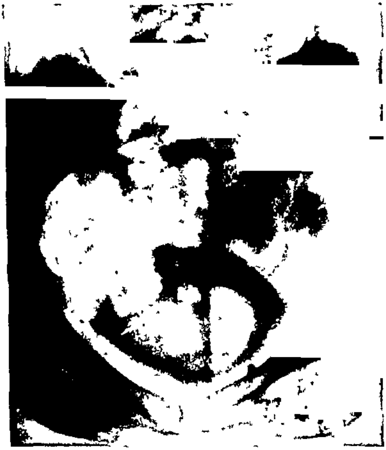

FIG. 1

Transversal incision of peritoneum from one edge of the pelvis to the other, just above the vesico-uterine blind alley. The ureters were normal; they were cut off, close to the bladder. The uterus, bladder and anterior face of vagina were removed, while all the pelvic cellular tissue was taken off. Implantation of the ureters into the sigmoid was accomplished by the Coffey II technique. The operation was concluded with a suture of the lower edge of the anterior peritoneal fold to the circumference of the upper passage to exclude pelvis, sigmoid and rectum from the abdominal cavity. Drainage was provided through the hypogastrium and the vagina.

Examination of the bladder showed that the tumor was white and embossed, with a firm consistency; its base of implantation was about 5 cm. in diameter, situated on the lower part of the posterior wall (fig. 2). Histological examination confirmed the diagnosis of leiomyosarcoma (fig. 3, 4).

The operative courses have been simple. Drainage ceased on the seventh

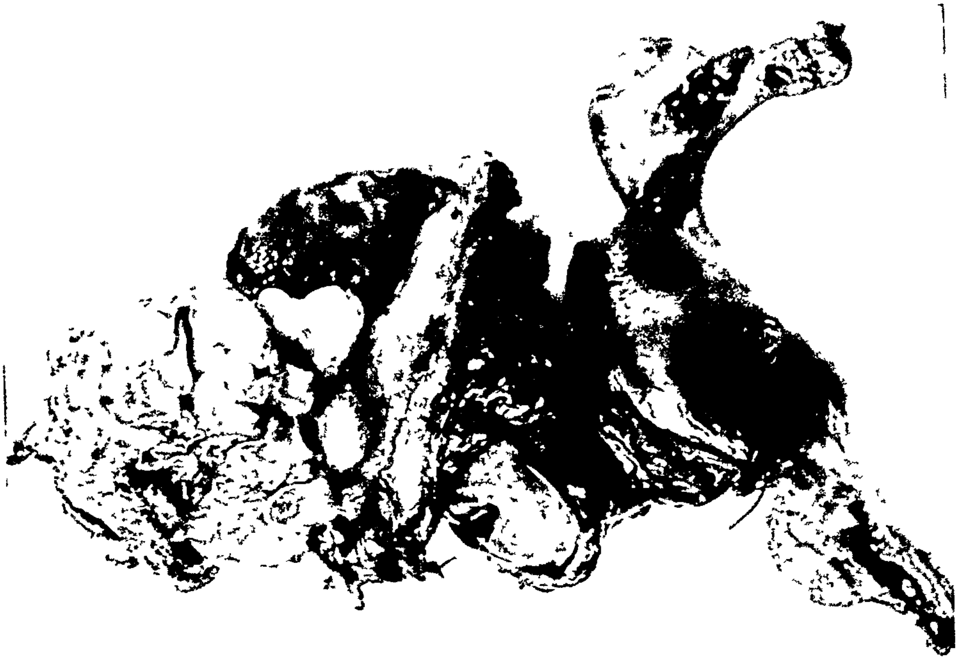

Fig. 2

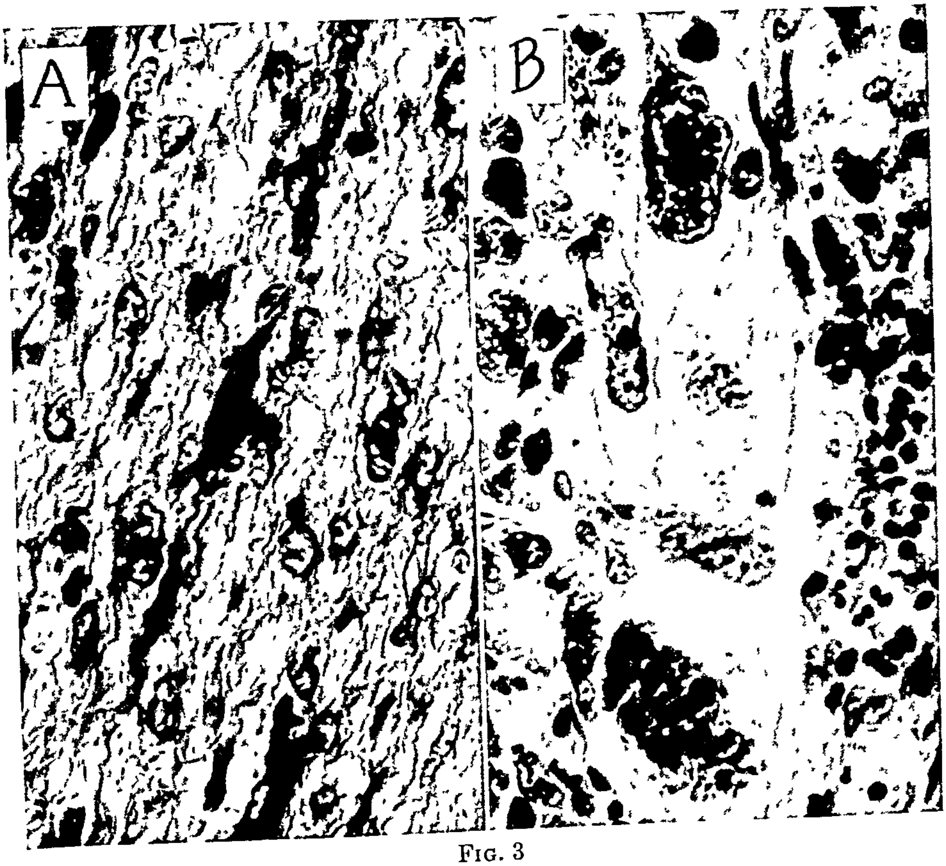

Fig. 3

day and ureteral catheters were removed on the thirteenth day. The patient left Pavillon V on May 29 (the thirty-first day). Urography showed a slight dilatation of ureters (fig. 4, *A*).

The patient has been followed at yearly intervals, the last time on June 14, 1952. Micturition occurs twice at night and from three to four times during the day. On palpation and vaginal examination, there are no signs of recurrence. In the last months of 1948 she had two outbreaks of fever; two also, in 1951. Urography in 1950 showed a slight calyceal-pyelo-ureteral dilatation on the right side; on the left, nothing abnormal. Urography in 1951 and again in 1952 showed that the right kidney did not eliminate Tenebryl any longer, but the elimination was perfect on the left, without any alteration in the excretion (fig. 4, *B*). Those *clichés* strikingly demonstrate the risks of ureterosigmoid implantation; at the moment of operation both ureters were normal, they have been implanted according to a similar technique; from one side the renal excretion has disappeared at the end of 3 years, on the other side it remained perfect 4 years later.

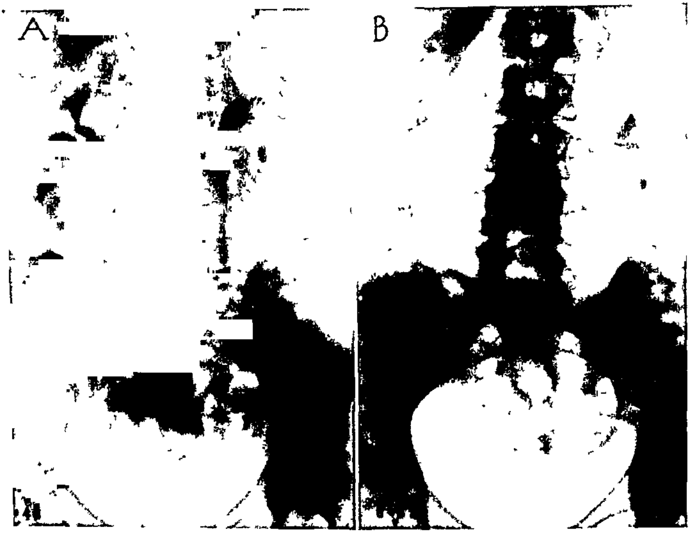

FIG. 4

Mr. Ch., aged 65 years, was admitted in Pavillon V on February 14, 1944 for hematuria since November 1943. He voided three or 4 times at night; during the day the intervals varied from 30 minutes to 2 hours; the act was painful, and sometimes dysuria was present. Cystoscopy disclosed a vesical tumor on the right side covered by a sphacelic coating and with a pedunculated appearance. When the bladder was empty it could be easily felt by recto-ab-

PRESENT STUDY

The present study was prompted by two observations. Hitherto, no one had studied blood loss quantitatively in the period following all types of prostatic surgery. Also, a marked difference in postoperative bleeding and in the physical and mental state of patients undergoing different types of prostatectomy has been noted in the past. This work is a study of 55 consecutive unselected cases treated by all types of open prostatic surgery and transurethral resection.

METHOD

Collections of all drainage, irrigations, dressings, linens, and bed clothes were immediately instituted upon the arrival of the patient in his room from the operating room. The material for determination of postoperative bleeding was saved in much the same way as that for the previous operative blood loss study, except that only 500–1000 cc of 0.4 per cent ammonium hydroxide solution were placed initially in the containers. These collections were examined at 18 or 24 hours after the patient's return from the operating room and then continued in 24-hour periods until all bleeding had ceased. In the case of transurethral resections, of course, only catheter drainage and irrigations were obtained. Several rinsings with the dilute ammonia solution were sometimes necessary to remove the stains from linens and gauzes. Whenever unbroken clots remained in the drainage collection, they were expressed by rolling in several layers of gauze with repeated soaking in dilute ammonia. After all sources of lost blood were hemolyzed and thoroughly mixed, the total volume was measured and a 5 cc aliquot taken for hemoglobin determination by a modification of the Wong hemoglobin iron method. If the mixture appeared too dilute to allow accurate analysis from 5 cc, a larger aliquot was concentrated to 5 cc by gentle heating on an electric hot-plate. The samples were treated with 5 cc of concentrated sulfuric acid and 2.5 cc of saturated potassium persulfate after which the usual steps of the Wong procedure were followed, and the red color, developed on the addition of potassium thiocyanate, read in a Klett-Summerson photo-electric colorimeter. As it was found that the protein free filtrates from samples containing urine and considerable amounts of cellular debris were frequently not completely colorless, a "zero" colorimeter reading was obtained on each tube of filtrate before the addition of the color producing reagent. Sample readings were then corrected for their "zero" as well as for the blank. A 0.5 cc sample of the patient's blood drawn on the day after operation was diluted with 4.5 cc of 0.4 per cent ammonium hydroxide and analyzed in the same way as the collection mixture. By comparison with a standard iron determination, in which the equivalent of 50 mg. per cent of iron in blood represented 14.6 gm. per cent hemoglobin in blood, the corrected colorimeter readings were converted to hemoglobin values. Using the simple formula:

$$\frac{\text{Total grams hemoglobin in the collection}}{\text{Grams \% hemoglobin in blood}} \times 100,$$

the equivalent volume of the patient's postoperative bleeding could then be derived.

RESULTS

In this study, the duration and volume of bleeding were greatest in one stage suprapubic prostatectomy, averaging 4.2 days and 513 cc. Next highest was second stage suprapubic prostatectomy with 2.7 days' duration and 276 cc blood loss. In simple perineal prostatectomy bleeding lasted 1.6 days with 153 cc of blood loss. The radical perineal prostatectomy cases averaged 0.9 days, and lost only 83 cc of blood. Similarly, in retropubic prostatectomy, the duration of bleeding was 0.9 days and blood loss 72 cc. Only two retropubic prostatectomies were in this series. The transurethral resection group had only 0.9 days of postoperative bleeding and the smallest volume of blood loss, 42 cc. However, no transurethral resection larger than 30 gm. was performed.

TABLE 1. *Summary of blood loss following prostatic surgery*

TYPE OF OPERATION	NO OF CASES	AVE AGE	GRAMS TISSUE RESECTED		CC. BLOOD LOSS				AVE NO. OF DAYS	
					First Day		Total		Duration Bleeding	Postop Hospital'n
			Ave.	Range	Ave	Range	Ave	Range		
One stage suprapubic	18	64.7	50.8	7–145	290	48–925	513	52–1700	4.2	20.9
Two stage suprapubic	6	64.2	58.2	28–85	154	3.5–328	276	4–953	2.7	18.8
Simple perineal	11	67.7	44.3	15–72	139	1–555	153	1–593	1.6	19.9
Radical perineal	3	69	105.0	70–170	83	5–230	83	5–230	0.9	18.7
Retropubic	2	70	26.0	23–29	72	33–110	72	33–110	0.9	14.0
Transurethral resection	13	63.8	10.6	1–30	36	0–80	42	0–148	0.9	7.8
Perineal exposure with biopsy	2	50.5	Biopsy		11	3–20	11	3–20	0.75	10.5

No relation between weight of tissue resected and postoperative blood loss was seen. The age distribution, weight of tissue, and length of postoperative hospital stay are shown in the table. When the duration of bleeding was 18 hours or less, the maximum time has been indicated as 0.75 day. Since study of the preoperative blood pressures disclosed that they had no bearing on the course of postoperative bleeding, they have been omitted from the table.

DISCUSSION

The large blood loss during the operation in the perineal procedures, as reported in a previous study, was unusual in our experience. As has been pointed out, the average loss would have been somewhat less if it had not been for one case which presented considerable difficulty and more profuse bleeding. Our subsequent experience tends to bear out the lower figure. However, accepting the average of that entire group, it is interesting to note that after operation the findings were reversed. The paucity of postoperative blood loss in the perineal group may be a large factor in the smooth convalescence of these patients. The very small blood loss following radical perineal prostatectomy was gratifying despite the fact that a considerably greater amount of tissue was removed during a much more extensive operation. In this operation, the bladder is anastomosed to the membranous urethra and all bleeders can be effectively sutured under direct vision. Added to this is the factor of patient comfort, as shown by a dearth of pain, distension or nausea, and the ability to eat and ambulate early. The ease of exposure, lack of vesical spasms, and absence of an abdominal incision may help to explain this observation. This is certainly equally true of the transurethral group. The retropubic patients are quite comfortable postoperatively. But, those undergoing suprapubic prostatectomy usually appear the most uncomfortable and lose the largest volume of blood after operation. The addition of hemostatic devices may potentiate spasms and deter contraction of the bleeding area, as postulated by Goodyear and Beard.

In the final analysis, each of the varied types of prostatectomy should be mastered and used when properly indicated by the complete urological surgeon. Adequate replacement of blood loss with whole blood is of great importance. Careful dissection and attentiveness to bleeding at the time of operating will remain the most important aids towards reducing the loss of blood both at the operating table and in the patient's room later. See table 1.

SUMMARY

A study of postoperative blood loss in 55 patients undergoing all types of prostatectomy was presented.

Blood loss was great following only one stage suprapubic prostatectomy. Next largest in quantity was second stage suprapubic prostatectomy.

Blood loss after simple perineal prostatectomy was one third that of the suprapubic methods, while that after radical perineal prostatectomy or retropubic prostatectomy was approximately one half of that of the simple perineal approach.

The postoperative blood loss in transurethral resection was the least of all the methods.

The above studies can serve as a guide to the requirements for whole blood administration to patients during postoperative periods.

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GENITO-URINARY TRACT INFECTION, PROSTATIC CALCULI AND CARCINOMA OF THE PROSTATE

ALEX L FINKLE

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Md

Previous reports[1, 2] have specified in equivocal terms a probable relationship between antecedent genito-urinary tract infection, particularly chronic prostatitis, and the subsequent formation of calculi in the prostate gland In 1927, Thomas and Roberts[3] traced the history of the dispute as to whether corpora amylacea or infection were independently the nidus of calculous formation within the prostate After citing proponents of each theory, they themselves concluded that " chronic prostatitis aids and abets the formation of calculi and the deposition of salts (on corpora amylacea) is merely secondary " Moore, in 1936, offered diffraction, chemical and histochemical data as the basis for his contention that corpora amylacea and prostatic calculi were fundamentally identical[4] He decided that "the evidence that (prostatic) calculi are directly related to infection is not well established "

The co-existence of prostatic calculi and carcinoma of this gland is still generally regarded as rare However, in 1944, Cristol and Emmett sought to dispel this notion by reporting an almost equal incidence of prostatic calculi, namely about 7 per cent, in 288 cases of benign prostatic enlargement and in 43 cases of prostatic carcinoma[5] The urologist today still commonly rejects any serious suspicion of carcinoma of the prostate, in the presence of rectally palpable induration and especially "crepitation" of the gland, when radiographic evidence of prostatic calculi is found This attitude is probably traceable to Kretschmer's statement in 1927, to the effect that the difficulty in distinguishing between prostatic carcinoma, tuberculosis or calculi by rectal examination can be resolved by radiological study, i e , " differentiation by means of the roentgen ray has always proved successful "[6] The modern diagnostic aids of serum acid phosphatase[7] and of open perineal prostatic biopsy[8] for corroboration of questionable carcinoma of the gland warrant serious reconsideration of this broad statement

The antibiotic era of the past several years may effect a marked change in the

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Present address Delafield Hospital Division, Columbia University College of Physicians and Surgeons, New York, N Y

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ultimate sequelae of long-standing genito-urinary tract infection. In order to provide a "base line" for future reference on this score, and for purposes of evaluating the concomitance of prostatic calculi and prostatic cancer as either coincidental or significant, the present study was undertaken.

SOURCE OF DATA

1) Clinical records. All case histories with mention of prostatic calculi recorded in the Brady Urological Institute of the Johns Hopkins Hospital during the preceding half-century were reviewed. The onset of long-standing genito-urinary infection was in most instances inferred from the history of signs or symptoms as stated by the patient. While this provided an obviously inaccurate figure for duration of nonspecific infections, the age at which the patient contracted a gonorrheal infection was usually well recalled. Clinical records of a number of patients were available for review of previous treatment rendered in this Institute at a youthful age; the finding of prostatic calculi years later in these instances was thus better demarcated as to duration of the disease. Often, in such cases, as well as in others treated elsewhere, infection developed for the first time after some genito-urinary surgical procedure. The date of onset of the infection was then firmly established.

The diagnosis of prostatic calculi was established by rectal examination, by roentgenography, by cystoscopic observation, by visualization at surgery and by dissection of the surgical specimen in the pathology laboratory. No cases were included in the present study if only unconfirmed diagnosis by rectal examination was rendered. Histologically defined calculi, so-called "microcalculi" were excluded from this survey in order to obviate the possibility of confusion between corpora amylacea and calculi.

In reference to data correlating calculi and cancer of the prostate it is emphasized that only those cases having *histological evidence* of carcinoma are included in the present analysis.

2) Autopsy data. A review was made of the autopsy reports of the hospital for the period June 1900, to June 1950, in which mention was made of either calculi or carcinoma of the prostate. This necropsy series would have excluded patients who died of genito-urinary disease or complications thereof at the Brady Urological Institute. In other words, the existence of prostatic calculi or cancer was to be an incidental finding recorded in the autopsy protocol. No association was to be sought between history of genito-urinary infection and the fortuitous discovery of prostatic calculi in the autopsy survey.

It proved impossible to identify from the records the size of intraprostatic calcifications accepted by the individual autopsy surgeons or pathologists as calculi. Furthermore, there was no way of knowing whether each of these pathologists had made note of the incidental finding of prostatic calculi in his autopsy records during the past 50 years*. Both of these facts so weakened the validity of the data of the postmortem series that it was decided not to analyse this source of material. The present paper is composed only of analyses of clinical records.

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* During the period June 30, 1900, to June 30, 1950, 20,907 autopsies were performed at the hospital. Increased emphasis upon the search for prostatic carcinoma (and thus of other prostatic disease, such as calculi) was noted after Rich's publication in 1935, of 14 per cent unsuspected prostatic cancer found in 100 autopsies of men over the age of 50 years.[9]

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RESULTS

Prostatic calculi. From the date of the first case history written by the late Dr. Hugh H. Young in September 1900, and all other records thereafter incorporated in the files of the Brady Urological Institute, a total of 45,891 charts were collected by June 30, 1950. These records included both out-patient and hospitalized cases, ward and private alike. However, this figure excludes charity out-patients who never entered the hospital as a bed-patient. A single history number was assigned regardless of the number of return visits or hospitalizations of a given patient and irrespective of the number of years elapsing between separate observations at the hospital.

There were 361 cases of calculi of the prostate found during a 46-year period. (The first record of prostatic calculi was dated February 1904.) This represents an incidence of 0.78 per cent of all urological records at the Brady Urological Institute. From September 1900, to June 30, 1950, there were 10,673 cases of benign prostatic hypertrophy recorded at the Institute. The presence of prostatic calculi in relationship to the gross incidence of benign prostatic hypertrophy encountered here was therefore 3.38 per cent.

Histological report on the prostatic tissue removed along with the calculi was made in 141 of the 361 cases. A total of 152 prostatic surgical procedures were done in these cases, being mainly enucleations by various routes, or transurethral resections. No histological reports could be found in 7 records; in 4 instances perineal prostatolithotomy constituted the entire operative procedure.

Prostatic calculi plus cancer. Of 141 histopathological reports on glands containing calculi, 20 showed adenocarcinoma of the prostate. This comprises an incidence of 14.18 per cent of cancer and calculi proved to exist concurrently in the prostate. Although the proportion of the 361 cases of prostatic calculi in which cancer was unexpectedly discovered is only 5.54 per cent, the lack of tissue specimens in 220 cases nullified the significance of the lower figure.

In the files of the Institute, up to June 1950, there were 2,304 cases of prostatic cancer and 1,996 cases of nephrolithiasis. Recalling that there were 10,673 cases of prostatic enlargement, it is readily seen that a ratio of about 5:1 existed between benign prostatic hypertrophy and prostatic cancer in patients entering for diagnosis and treatment. A roughly similar ratio appears between renal calculi and prostatic calculi. These figures possibly suggest a greater overall frequency of both prostatic calculi and of prostatic cancer, separately and coexistently, than generally appreciated.

Age incidence of prostatic calculi. Prostatic calculi were found in men between 17 and 87 years of age in this review. At a somewhat older age the youngest case of co-existing prostatic cancer was recorded. Table 1 summarizes the data according to age-decade in which the diagnosis of prostatic calculi and also calculi plus cancer were established.

It may be noted that prostatic calculi were most frequently diagnosed in the sixth decade whereas co-existing calculi and cancer of this gland were found most often in the seventh decade of life.

Racial groups. Of the entire series of 361 patients, 337 were Caucasian, 23 were Negro, and 1 was Oriental. Among the 20 cases of cancer with calculi of the prostate, 18 were white and 2 were colored men.

These figures of racial membership do not reflect either the in-patient or out-patient ratio of white-to-colored patients at this Hospital. No figures were available as to those patients with prostatic calculi for whom hospitalization had never been ordered. Such out-patient charts were not studied for this review. Finally, no breakdown as to race was made of the total numbers of benignly hyperplastic or carcinomatous prostates recorded in the Institute; this prohibited an attempt to analyse the proportion of white-to-colored patients having these respective diseases.

TABLE 1. *Frequency distribution by age of prostatic calculi and calculi with cancer*

PROSTATIC CALCULI		PROSTATIC CALCULI WITH CANCER
Age in years	No. of cases	
11–20	1	
21–30	10	
31–40	22	
41–50	76	2
51–60	107	2
61–70	96	13
71–80	40	2
81–90	9	1
	Total:.... 361	Total:....... 20
Range: 17–87 years		Range: 50–81 years

TABLE 2. *Methods of diagnosis of prostatic calculi, 361 cases*

METHOD	CASES
X-ray only	143
X-ray plus palpation, cystoscopy or surgery	187
Palpation and cystoscopy without surgery	66
Total number surgical operations	152
Prostatolithotomy only	4
Total number histopathological reports	141
No pathology report found	7

Diagnostic techniques. Combinations of the various diagnostic methods by which prostatic calculi were identified would provide innumerable and confusing data. Table 2 represents an effort to simplify the most salient figures within this section.

In essence, observation of prostatic calculi by x-ray, often verified cystoscopically, proved to be the most common means of recognizing this pathological change. Roentgenography was the sole diagnostic measure in 143 cases. The second most frequent form of diagnosis employed several techniques, such as the roentgenogram and rectal palpation, or the x-ray with either cystoscopic, surgical or specimen-dissection confirmation of the presence of calculi. Two or more of these methods were used in 187 patients. Actually, in many of the patients only 2 of these examinations led to the diagnosis, and no surgery was done. In other instances, 2 diagnostic approaches were recorded, one of which was surgery. Thus, 66 nonsurgical diagnoses of prostatic calculi were cited. Even when surgery was performed, the calculi might not have been seen in the operating room; subtotal prostatectomy would remove the surgical capsule of the prostate intactly,[10] leaving direct visualization of the calculi to the pathology laboratory. At any rate, 152 surgical procedures were carried out in this series.

As indicated from the foregoing qualifications, these figures have significance *per se*, and not in direct relationship to the other data presented in the table.

TABLE 3. *Duration of urinary tract infection, by case history, 258 cases*

	DURATION OF INFECTION						
	Months					Years	
	1–12	13–24	25–36	37–48	49–60	5–10	Over 10
Number of cases...........	79	25	14	13	21	50	56

Unusually Long Infections

YEARS	NO. OF CASES
20–30	20
31–40	3
41–50*	1

* Longest, 50 years: chronic prostatitis

Incidence of urinary tract infection. In 258 charts, urinary tract infection could be gleaned from the history of the given patient. In 2 other cases, urinary tract infection was mentioned, but no duration could be ascertained from the chart. Most often, urethral stricture treated by passage of sounds for dilatation, or some form of surgery previously done on the genito-urinary tract provided a known history as to onset of urinary infection. A more or less documented duration of infection, embracing periods of 1 month to 14 years, was excerpted from 55 of the records. But not all such cases had had x-ray study at the outset, and this minimum criterion for the existence of prostatic calculi was lacking. The cases of known temporal relationship between calculi and infection, included in the 55 authenticated cases, are indicated later.

The total picture of the incidence of urinary infection, undifferentiated as to pre- or post-existence of calculi, or as to laboratory proof of infection is compiled as table 3.

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[10] Henline, R. B.: J. Urol., 44: 146–168, 1940.

Although criticism patently applies to inability to identify the onset of the urinary infection, it appears significant that 71.46 per cent of the 361 patients reviewed had such infection. Since prostatic calculi can exist without producing infection[10] and since 41.09 per cent of these patients harbored infection for 5 years or longer, the likelihood that infection could be the nidus for prostatic calcification is greater than not.

From the viewpoint of statistical correlation, the data as to urinary infection in this survey are inadequate. It would be necessary to know the incidence of such infection in the 10,673 patients who had benign prostatic hypertrophy without calculi in order to relate to this population group any causal connection of antecedent infection to later development of prostatic calculi.

In table 4, the influence of urinary infection as to the later development of calculi (a contested issue) and the association of infection with prostatic calculi (a rather generally accepted tenet) are depicted numerically.

TABLE 4. *Known time relationship: prostatic calculi and urinary tract infection, 22 cases**

Calculi preceded infection	8
Calculi followed infection	12
Calculi and infection of equal duration	1
Calculi without infection	1

* Includes 4 cases having both calculi and cancer of prostate concomitantly.

TABLE 5. *Years elapsed between contracting gonorrhea and diagnosis of prostatic calculi, 181 cases*

No. of years	1-10	11-20	21-30	31-40	41-50	51-60
No. of cases	10	23	46	49	32	21

Age range of primary infection: 13-57 years.
Most cases infected before age of 20 years (96 cases).
Second most common age of infection, 21-30 years (58 cases).

From the small number of cases in which the duration of the infection and the existence of the calculi were both known, no conclusion may be validly drawn. Although one-third more of the patients in this group gave a positive history of antecedent urinary infection in relationship to prostatic calculi than did those forming calculi before infection, this finding is restricted to this study and broad generalization is to be avoided.

History of gonorrheal urethritis. Although the history again must be relied upon in an attempt to correlate genito-urinary infection with the later appearance of prostatic calculi, a Neisserian urethritis was usually vividly recalled by the patient. There was certainty as to its existence, although occasionally vagueness as to the exact age of infection. Table 5 incorporates pertinent features of this aspect of the survey of 361 cases of prostatic calculi, including the 20 cases of co-existing calculi and cancer of the gland.

Excluded from the preceding group are 17 cases in which no record of questioning the patient about venereal disease could be found in the chart, and 2 patients who were quoted as having had the disease without any mention as to age of the initial infection. The number of cases with an acceptable history of gonorrhea constituted 50 per cent of the total group of prostatic calculi in this study.

When multiple Neisserian infections were recorded, the age at which the first occurred was used in calculating the time elapsed between such infection and the later appearance of prostatic calculi.

Gonorrheal infection was contracted generally before 20 years of age, while prostatic calculi were found most frequently in the 51- to 60-year-old group of men. In those patients in whom prostatic calculi were known to have developed after the existence of urinary tract infection, long latent periods were noted before calculi appeared in the prostate. But gonorrheal infection at the youthful age did not bear relationship to later urinary infection due to a variety of bacterial invaders. In brief, the acute gonorrheal disease, even though present for 1 to 3 months in most of these patients during the pre-antibiotic days, did not predispose to general types of urinary tract infection later in life.

TABLE 6. *Incidence of gonorrhea in United States, 1920–1950*

YEAR	TOTAL CENSUS	TOTAL NO. CASES G. C. REPORTED*
1920	106,466,000	172,387
1930	123,077,000	155,875
1940	131,936,000	175,841
1941		189,772 (84,795)†
1942		213,071 (73,804)
1943		275,648 (85,903)
1944		300,585 (95,809)
1945		284,944 (73,575)
1946		364,853 (97,371)
1947		400,659 (97,758)
1948		363,014 (82,588)
1949		331,695 (68,264)
1950‡	151,240,000	233,919§ (40,741)

* Includes military cases. Incorporates total undifferentiated report: figures not classified as to color and sex 1915–1930 by U. S. Public Health Service.

† From 1941 on, incidence of G. C. specified as to white civilian males (in parentheses) in addition to total, undifferentiated figure.

Total and white civilian male data for 1941 only are less than actual, since gross figures from Iowa excluded.

‡ Census figures from *Statistical Abstract of the United States*, U. S. Dept. of Commerce, Bureau of Census, Washington, D. C. 1951, p. 8.

§ Data for 1950 incomplete, since last quarter of fiscal year omitted here. Statistics on gonorrhea kindly supplied by Division of Venereal Disease, U. S. Public Health Service, Federal Security Agency. Publication here authorized by Dr. Theodore J. Bauer, Medical Director and Chief of Division of Veneral Disease.

National statistics on gonorrhea. In order to compare the 50 per cent incidence of gonorrheal histories disclosed in this survey with the occurrence of the disease in the population-at-large, those latter data were acquired. Table 6 presents these figures.

Aside from uncontrollable variables and weaknesses in the compilation of the foregoing information, it is clear that the 50 per cent incidence of gonorrhea in the present survey of 361 cases of prostatic calculi exceeds by far the occurrence of that disease in the general population, even during the years when the patients now under study were infected. Unfortunately, the incidence of gonorrheal history in the 10,673 patients of benign prostatic hypertrophy studied at this Institute *who did not develop calculi* is not known.

The figures in table 6 reflect improved methods of collecting and accumulating public health data, the influence of war years on spread of gonorrhea and possibly the beginning decline in occurrence of the disease as an effect of the chemotherapeutic and antibiotic era.

Unrelated diseases found in present survey. Because the group of patients in whom prostatic calculi appear often suffer other "diseases of aging", it seemed worthwhile to determine if any given illness or specific group of infirmities existed. That this was not so is demonstrated in table 7.

TABLE 7. *History and diagnosis of some common diseases in patients with prostatic calculi*

1. Genito-urinary

PENIS	URETHRA	SCROTUM	TESTIS	EPIDIDYMIS	SEMINAL VESICLE	BLADDER	URETER	KIDNEY
2	45	11	5	23	6	50	12	56

2. Systemic

ENDOCRINOPATHY			C-V-R	LUES	ARTHRITIS	TB	EYE
Diabetes	Thyroid	Parathyroid					
7	5	1	63	28	11	5	6

With regard to the emphasis on various genito-urinary diseases specified in the above table, it is manifest that a urological institute would record most carefully any associated or historical pathological change in this bodily system. The penile lesions were hypospadias; the urethral were mainly strictures; the scrotal were either hydrocoele or varicocoele; the testicular were traumatic, surgically excised or inflammatory; the epididymal were chiefly inflammatory—as was also true of the seminal vesicular lesions; the bladder, ureteral and kidney diseases were infectious, congenital and calculous for the most part.

No single group of generalized diseases in these patients were even suggestively related to the prostatic calculi. The cardiovascular-renal (C-V-R) lesions were probably less frequent than in other hospitalized men of this age. Syphilis appeared to be a fortuitously concurrent disease and to bear no relationship to formation of prostatic calculi in later life.

Other body sites of cancer and calculi. Whether prostatic calcification or cancer developed in any relationship to cognate pathological changes in other tissues appears numerically unlikely, according to the figures composing table 8.

From these data it can not be deduced that prostatic calculi are part of a generalized, systemic process of pathological calcification throughout the body. That genito-urinary tract cancers are recorded most frequently suggests that these areas were more thoroughly investigated than others in this specialized Institute However, when indicated in any patient, a search for cancer anywhere in the body was made It would appear that only large or otherwise impressive skin cancers were mentioned, since a greater incidence of cutaneous neoplasms than recorded here would be expected in men of this age group [11] The locations of the extra-urinary tumors do not point up any connection between them and urological neoplasms

TABLE 8 *Cancer and calculi elsewhere in patients with prostatic calculi*

Cancer (11 cases)

BLADDER	SKIN	URETHRA	LIVER
7	2	1	1

Calculi (71 cases)

KIDNEY	BLADDER	URETER	URETHRA	GALLBLADDER	PANCREAS
37	19	11	2	1	1

Twelve cases had calculi in 2 other locations (also in genito urinary tract) One case had calculi in 3 other sites (renal, ureteral, vesical) One case of hyperparathyroidism had bladder and pancreatic calculi, in addition to the prostatic calculi

TABLE 9 *Summary of data Co existent prostatic calculi and cancer*

Number of cases	20
Race	
White	18
Negro	2
Calculi diagnosed by x ray and confirmed by surgery	15
Diagnosis confirmed by histopathology (subtotal perineal prostatectomy)	5
History of urinary tract infection (duration 1–13 years)	11
History of gonorrheal urethritis (excludes 1 case lacking proper notes)	6
Known existence of calculi (3–10 years before cancer diagnosed)	4
Calculi concurrently elsewhere in body (2 kidney, 1 bladder)	3
Cancer simultaneously elsewhere in body*	1
Histopathological mention of benign prostatic hypertroply (ages of cases where hyperplasia not mentioned 50, 61, 62, 64, 72, 81)	14

Other diseases commonly present, mainly cardiovascular and arthritic Only one case of lues

* Bladder cancer had been known and treated for 10 years before discovery of prostatic cancer in gland containing calculi

Collected data on prostatic calculi with cancer All the features accumulated previously for prostatic calculi are indicated for the concomitance of calculi and cancer of the gland and are compiled in table 9

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[11] Ackerman, L and del Regato, J A *Cancer Diagnosis, Treatment and Prognosis,* St Louis C V Mosby Co , 1947, pp 18–19

The foregoing itemizations provide no remarkable facts and are more or less similar to those disclosed in the analysis of the entire group of 361 cases of prostatic calculi.

Miscellaneous observations. Of the 121 cases reported histopathologically as benign prostatic tissue, 99 were specified as "benign prostatic hypertrophy", 19 were described as "chronic prostatitis" and 3 as "normal prostate". The latter group pertained to patients 43, 44 and 46 years of age. It would seem that even these younger patients' prostatic tissues should show some evidence of hypertrophy, but presumably this change was negligible or minimal in comparison with most specimens examined, and was therefore ignored by the pathologist.

Included in the 20 cases harboring both calculi and cancer in the prostate were 4 cases in which an earlier histopathological report on the operated gland was benign, 4, 6, 7 and 10 years previously. Three other cases, not included in the group of 20, developed metastases from prostatic cancer proved by x-ray evidence and by elevated serum acid phosphatase within 3, 4 and 8 years after the first surgical procedure for benign prostatic hypertrophy. These latter cases did not receive secondary prostatic surgery.

The delayed diagnosis in 7 cases of prostatic cancer may represent failure at the first operation to have removed prostatic tissue bearing the malignancy, failure of the pathologist to diagnose the neoplasm originally, or development of the cancer in the residual (posterior) surgical capsule left at the time of the first operation. Rolnick remarked that "the finding of carcinoma following enucleation in apparently benign hypertrophy has been reported to vary between 5 and 15 per cent".[12] Since, in the present survey, *all the prostatic cancer coexisting with calculi were undiagnosed pre-operatively, the finding of unexpected carcinoma was 14.18 per cent here.* Smith and Woodruff found that cancer developed in the residual surgical capsule of the prostate in 6 per cent of surgically enucleated glands, most often within 5 years after the original surgery.[13] Some of the 7 cases now under discussion in the present survey may represent *de novo* neoplastic growth developing years afterwards and unrelated to the first surgery for benign prostatic hypertrophy.

In the histopathological reports of the 141 tissue specimens reviewed in this paper, corpora amylacea were mentioned in 38 per cent. Because the writer did not himself study the microscopic sections in these cases, it cannot be stated in how many instances the pathologist neglected to specify the presence of these intracinar formations. Since the relationship of chronic prostatitis to the formation of corpora amylacea is debatable, no attempt was made to correlate a history of urinary tract infection with those tissue sections containing corpora amylacea.

The condition of the testicles was generally mentioned only clinically. Thus, relationship of gross testicular atrophy or of biochemical measure of testicular function to prostatic calculi or to coexistent prostatic cancer is lacking in this survey. In one case (B.U.I. No. 23723) there was an attempt to correlate testicular histology with prostatic pathology for another study.[14] There appeared to be no connection between testicular histology in patients found to have benign prostatic hypertrophy or cancer of the gland. It might be reasonably inferred from such data that testicular status was unrelated to formation of prostatic calculi. A study of testicular biopsies performed in patients found to have prostatic calculi might provide valuable information in this regard.

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[12] Rolnick, H. C.: The Practice of Urology, Philadelphia: J. B. Lippincott Co., 1949, p. 318.

[13] Smith, G. G. and Woodruff, L. M.: J. Urol., 63: 1077–1080, 1950.

A single case history, abstracted as to chronology of pathological developments, may elucidate many of the features illustrated in the present survey.

W. S. (B.U.I. No. 20572), a 61-year-old, white book salesman, was admitted in April 1950 complaining of progressively worsening symptoms of prostatism during the preceding 6 months. The past history had been recorded at this hospital since 1931 and may be summarized as follows:

1931: Hematuria and frequency developed after a 200-mile automobile trip in February. Ureteral catheterization at Brady Urological Institute revealed bilateral B. coli pyelitis 10 days later. No evidence of prostatic calculi by rectal palpation, cystoscopy or radiography. Prostatitis first diagnosed in May by rectal examination and microscopic finding of pus cells in expressed prostatic secretion. Follow-up revealed unchanged prostatitis in October. Then patient failed to return to hospital until 1932.

1932: Silver nitrate irrigations of bladder repeatedly given for cystitis (organism not specified). Prostatic smears at various intervals revealed 50–100 white blood cells per high power field and "decreased lecithin." Cultures of urine from each kidney reported as sterile.

1934: Mercurochrome (3 cc of 3 per cent solution) injected directly into prostate per perineal route on several occasions failed to reduce number of white cells in prostatic secretion.

1936: Symptoms of backache persisted. The chronic prostatitis and cystitis failed to respond to oral mandelate therapy. Rectal examinations of the prostate recorded "the lateral lobes firmer than normal in consistency and irregular in form." Expressed prostatic secretion showed 30–40 white blood cells per high power field. Colon bacillus recovered from left ureteral urine in February, despite ketogenic diet. Hospitalized briefly in February, at which time right pyelitis with a "gram-negative bacillus" was found. Chronic prostatitis persisted (15–20 white blood cells per high power field), unaffected by oral medication with Phospho-Mandelate.

1937: Urotropin exerted no favorable influence upon the chronic urinary tract infection. Expressed prostatic secretion showed 15–20 white blood cells per high power field. Dull, constant low back pain recurred as primary symptom of prostatitis. Sulfanilamide was given orally over a 3-month period, without favorable result. In the expressed prostatic secretion 40–50 white blood cells per high power field were still present after treatment in various dosage levels.

1938: Use of oral sulfanilamide for right choroiditis (20 gr. daily for 3 days) produced a sensitization reaction consisting of swelling of the lips and generalized formication. Chronic prostatitis with dull, low back pain persisted.

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[14] Lynch, K. M. and Scott, W. W.: J. Urol., 64: 767–776, 1950.

1939: *Prostatic calculi* seen by x-ray examination for the first time *after 8 years of known prostatitis.* Intraprostatic injection of 10 cc of 10 per cent mercurochrome given without benefit for persistent chronic prostatitis. Culture of bladder urine revealed colon bacilli and atypical Aerobacter.

1943: Expressed prostatic secretion revealed 50–80 white blood cells per high power field. Sulfadiazine was given orally for 2 weeks without appreciable symptomatic relief or improvement in the consistency of the prostate by rectal palpation.

1948: Expressed prostatic secretion "loaded with white blood cells." Low backache unabated.

1950: Symptoms of prostatism (weakness of urinary stream and sensation of inadequate emptying of the bladder) had become progressively annoying for 6 months. By rectal palpation the prostate was 1½ times enlarged. Induration and crepitation throughout suggested benign prostatic hypertrophy and prostatic calculi. Cystoscopy revealed a large median lobe and moderate lateral lobe hypertrophy, causing residual urine of 70 cc. X-ray studies confirmed the clinical diagnosis of prostatic calculi. A transurethral resection of the median lobe and of parts of the lateral lobes was performed in April 1950. Pathology Department reported carcinoma of prostate, prostatic calculi and benign prostatic hypertrophy. Oral stilbesterol was given (1 mg t.i.d.) for 6 weeks. Then a radical perineal prostatectomy was performed. Convalescence was satisfactory. Recovery of urinary continence was slow.

Histopathological report on total surgical specimen same as for transurethrally removed tissue.

DISCUSSION

Conjecturally, the formation of prostatic calculi may be a deposition of earthy phosphates on corpora amylacea,[4, 15] which in turn may result from chronic prostatitis or cause chronic prostatitis.[11] Or the *inspissation* of prostatic acinar secretions induced by infectious ductal obstruction may produce calculi unrelated to corpora amylacea.[16, 17] The inorganic constituents resemble closely those in any urinary calculi, while the organic constituents are closely related to bone salts.[18] Endocrine influences may affect development of calculi as well as benign prostatic hypertrophy.[11] Metabolic alterations in the infected prostate or within the bodily economy of the aging male may predispose to this calcification. Little argument prevails regarding the extrusion of calculi toward the surgical capsule of the gland as the process of adenomatous hyperplasia proceeds,[10, 15, 18] whether the calcareous deposits be intra-acinar or parenchymal originally.

Of the preceding hypotheses, only that regarding the mechanical pathway leading to the final anatomical location of calculi is generally accepted. Although even this concept bears some basis for controversy, this problem is insignificant

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[15] Hamer, H. G. and Dykhuizen, T. A.: Am. J. Surg., 24: 119–123, 1934.

[16] Judd, E. S. and Crenshaw, J. L.: Minn. Med., 2: 52–56, 1919.

[17] Young, H. H. and Davis, D. M.: Young's Practice of Urology, Philadephia: W. B. Saunders Co., 1926, p. 382.

[18] Huggins, C. and Bear, R. S.: J. Urol., 51: 37–47, 1944.

as compared with the uncertainties that pervade the theories of formation of these prostatic calcifications.

When the present review was completed, it became apparent that some essential data were lacking in order to establish statistical correlations as to the role of infection in the later development of prostatic calculi. For example, the group of patients with only benign prostatic hypertrophy were not analyzed as to the presence or absence of antecedent urinary tract infection, and the patients within that category of prostatic hypertrophy who had gonorrheal urethritis at a youthful age and did not develop calculi were not studied in that regard. Nonetheless, within the limitations of the information presented, certain trends may be suggested.

Firstly, more than two-thirds of the patients in the present survey had a history of urinary tract infection—often for exceedingly long periods of time—presumably before prostatic calculi developed. Because one-half of the cases reviewed here had Neisserian infection relatively early in life, it is quite probable that the disease was a *nidus* for later intraprostatic deposition of calcium salts. Other reports cite an equally high incidence of gonorrheal histories, far greater than noted in the general population.[1, 3, 5, 6]

The age at which gonorrhea was most commonly contracted was much younger than the average age at which prostatic calculi were diagnosed. Although a small number of patients harbored radiographically demonstrable calculi at an early age, it is possible that the deposition of calcium salts in the prostate was for some reason accelerated in these individuals. However, this could not be correlated with any historical or biochemical data within their hospital records. On the other hand, there was no general relationship between pathological calcifications in soft tissues of patients found to have prostatic calculi.

Less than one-half of the histopathological reports rendered in 141 cases here made reference to corpora amylacea. The presence of benign prostatic hypertrophy was mentioned in 113 instances of the 141 prostatic tissue specimens removed from glands found to have calculi. The existence of corpora amylacea has been stated to be inversely proportional to benign hypertrophy of the gland.[4] Although this finding of association of corpora amylacea with smaller glands appears to find application in the present study of benign, calculi-bearing prostates, it does not hold in the cases of coexistent prostatic calculi and cancer. In the latter group, benign hypertrophy of the prostate is mentioned in almost two-thirds of the tissue specimens bearing prostatic calculi with cancer.

Hudson et al. observed that unsuspected prostatic carcinoma did not occur in smaller glands more frequently than in the larger, benignly hypertrophied specimens.[8] In the present study, this lack of correlation between small size of the prostate and development of adenocarcinoma was confirmed. Although the series of cases of cancer here is small, additional data from other sources should be reported and may be expected to corroborate this point.[19]

So-called "hormonal imbalance" could not be evaluated from the data

[19] Hudson, P. B., Finkle, A. L., Sproul, E. E. and Stout, A. P.: Prostatic cancer V. Detection of early lesions. In press.

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METASTATIC CARCINOMA OF THE PENIS SECONDARY TO CARCINOMA OF THE RECTUM: A REVIEW OF THE LITERATURE AND REPORT OF A CASE

HOBART L. BOYD

From the Department of Surgery, Division of Urology, of the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

A review of the literature revealed that metastatic growths in the penis, of all kinds and from all primary sites, were relatively uncommon and that there were but five authentic cases of penile adenocarcinoma secondary to a primary growth in the rectum. Niewiesch published the first case of this sort in 1933. This was followed by reports by Mathesan in 1935, Stein and Hantsch in 1937, Thompson in 1950, and Cattell and Mace in 1951. We have recently observed such a case in which the secondary penile lesion occurred five years following an abdominoperineal resection for adenocarcinoma of the rectum. Because of the apparent rarity of this condition, a sixth case will be presented in detail and pertinent data discussed from the cases to be found in the literature.

CASE REPORT

R. B. N., S. M. H. No. 257412, a 54 year old white man, was first seen in December 1946 with symptoms suggesting large bowel obstruction. Two years previously he first noted several loose bowel movements daily, containing mucus but no blood. During this period there was a gradual weight loss of 15 pounds accompanied by increasing fatigue and irritability. For several weeks the stools had been of small caliber and following the passage of stools he frequently noted bright blood on the paper. Three weeks before admission the patient became constipated, accompanied by shifting cramping sensations in the abdomen and almost constant dull low back pain. Throughout this entire period he had noted a slight decrease in size and force of urinary stream and occasional burning and nocturia.

The patient's general health had been excellent. He had pneumonia in 1942. Operations had been performed for anal fissure and hemorrhoids in 1944. He had an appendectomy for acute appendicitis in May 1946. The system review and family history were otherwise noncontributory.

Physical examination revealed a thin man who appeared chronically ill and showed evidence of weight loss. The vital signs were normal and the blood pressure was 148/86. No abdominal tenderness was elicited but there was mild gaseous distension with a visible and palpable dilated bowel above the sigmoid. On rectal examination the prostate gland was moderately enlarged, smooth and of normal induration. Above the level of the prostate on the posterior wall of the rectum was a firm, fixed, nodular mass. The mass seemed to be attached to the hollow of the sacrum.

This investigation was supported with funds from the Dr. Henry C. Buswell Memorial.
Read at annual meeting, Northeastern Section, American Urological Association, at sea, aboard the S. S. Ocean Monarch, October 4–10, 1952.

The laboratory examinations revealed the following the blood Wassermann was negative, red blood count 5,190,000, white blood count 8,350, hemoglobin 12 4 gm , serum nonprotein nitrogen 13 mg per cent, total proteins 6 5 gm per cent, and A/G ratio 5 2/1 3 The urine examination was completely negative for albumin, sugar, white blood cells, red blood cells, casts and bacteria An x ray of the abdomen showed slight dilatation of the large bowel in the region of the left transverse colon

A combined abdominoperineal resection of the rectum was performed by Dr T B Jones on December 16, 1946 No large glands were encountered within the abdomen but there was a small nodule on the under surface of the liver The nodule could not be visualized but on palpation did not seem to be a metastasis The pathological specimen consisted of a 24 cm segment of terminal bowel with a completely annular, stenosing lesion measuring 5 5 cm in length, located about 5 cm above the anus The specimen showed the bowel above the lesion dilated to a diameter of 12 cm Studies of the microscopic sections revealed a typical adenocarcinoma of the rectum with invasion deep into the muscular layers Metastasis was found in one regional lymph node (fig 1)

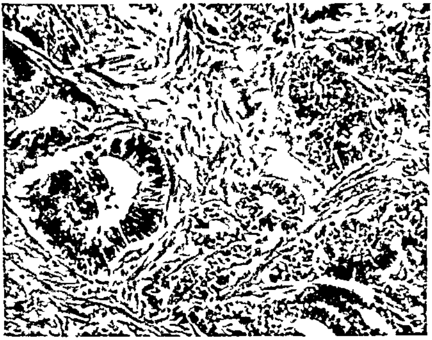

Fig 1 Section from primary adenocarcinoma of rectum showing invasion into muscle

Several complications arose during his immediate postoperative course Intestinal obstruction developed necessitating laparotomy for release of small bowel adhesions on the fourteenth day Urinary retention followed the removal of the Foley catheter which had been inserted at the time of surgery A cystoscopic examination revealed coarse trabeculation and a cystometric study demonstrated hypotonicity of the bladder The prostate gland showed moderate hypertrophy consisting of two lateral lobes and a median lobe which obscured the proximal one third of the trigone A transurethral resection of the prostate gland was performed on January 28, 1947 and recovery from the procedure was uneventful

The patient's perineal wound was slow in healing and 6 months after surgery a perineal abscess developed, necessitating readmission to the hospital for drainage. Biopsy studies of tissue from the perineal wound showed infected granulation tissue but no evidence of tumor. The perineal wound healed satisfactorily.

He was followed regularly thereafter by his general surgeon. On several occasions he complained of pain in the perineum but had no other symptoms until February 1951 when, in addition to the perineal discomfort, he noted burning with urination, increasing nocturia, occasional urgency and frequency. Examination revealed a very hard mass in the perineum just to the right of the midline under the symphysis near the base of the penis (fig. 2, *A*). With a sound in the urethra, the mass could be moved over the instrument and seemed anterior and lateral to the urethra. Microscopic examination of the urine revealed an occasional white and a rare red blood cell. He was re-admitted to the hospital and the mass explored. A very hard oval mass of tissue measuring 3.6 by 2.2 cm. was exposed through a midline perineal incision. It had invaded a large part of the right ischiocavernosus muscle, was in close proximity to the pubic ramus and had penetrated through Buck's fascia into the corpus cavernosum at one point. It was carefully dissected off the pubic ramus and the involved area of Buck's fascia and corpus cavernosum removed from the penis. Pathological studies of this tissue showed metastatic adenocarcinoma identical with the original rectal tumor (fig. 3).

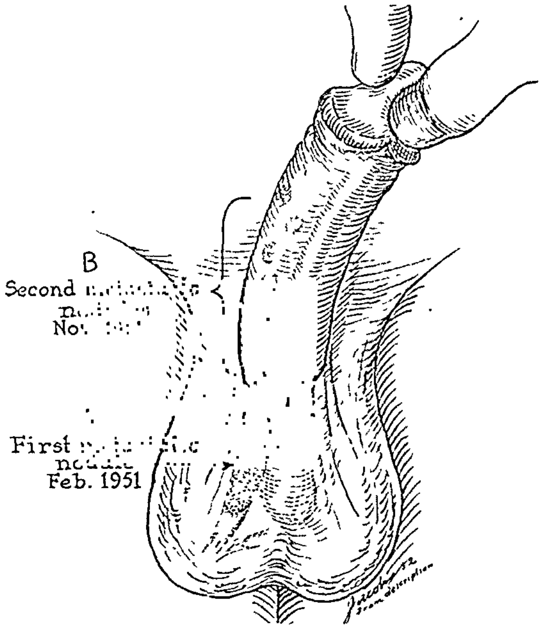

FIG. 2. Schematic drawing with A and B representing sites of first and second metastatic growths respectively.

The patient had no further trouble until October 1951 when he became aware of a painful nodule in the right side of the penis near the base. When he returned to see us in November 1951, one could not determine whether this mass which was palpable and freely movable over a sound was superficial to, or beneath, Buck's fascia. It was believed to be metastatic in origin but since the urine was heavily infected it seemed advisable to place him on a urinary antiseptic and examine him again 1 week later On this occasion at least two small areas could be palpated in or beneath Buck's fascia, and in addition there was a hard tender mass extending down along the right pubic ramus just about to the upper limit of the area previously explored A cystoscopic examination revealed a normal bladder and prostatic urethra without any evidence of tumor The blood counts were normal and the serum nonprotein nitrogen was 38 mg per cent A phenolsulfonphalein test showed 65 per cent excretion in 2 hours Acid and alkaline phosphatase studies were normal An excretory urogram showed good function bilaterally with no evidence of pathological change He was admitted to the hospital for radical amputation of the penis

The radical amputation of the penis was performed by Dr W W Scott on January 2, 1952 A midline incision was started several centimeters above the base of the penis over the abdomen, then carried downward encircling the base of the penis and extended a short distance along the median raphe The shaft of the penis was freed down to the bulbous urethra where the urethra was separated from the corpora cavernosa and severed Following this the dorsal penile artery and vein were cut and ligated and the crural attachments of the corpora cavernosa dissected off the pubic rami The bulbous portion of the urethra with corpus spongiosum, having been dissected free for a satisfactory distance was cut across and then transplanted through a stab wound in the perineum just under the scrotum Great care was taken to avoid angulation and tension of the urethra and a free cuff of urethra approximately one half inch in length was allowed to extend beyond the skin of the perineum A Foley catheter was inserted through the urethra for drainage Due to the previous surgery, considerable scar tissue was encountered in dissecting the crural attachment from the pubic ramus on the right side and also in separating the corpus spongiosum from the right corpus cavernosum At the end of the procedure, however, it appeared that all tumor bearing tissue had been removed The wound was adequately

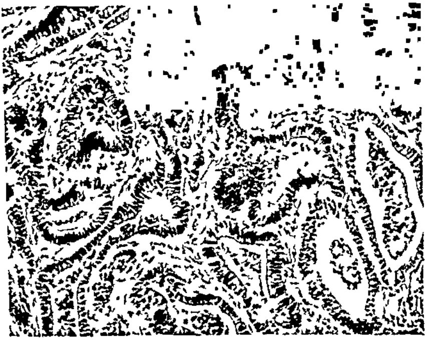

Fig 3 Section from metastatic nodule in ischiocavernosus muscle, removed by local excision, showing adenocarcinoma identical with primary rectal tumor

drained and closed. The patient's course was uneventful and he was discharged on the fourteenth postoperative day. Examination of the surgical specimen revealed no involvement of the glans penis or urethra. Within the right corpus cavernosum, in the proximal two thirds of the specimen, were 6 hard nodules measuring from 0.5 to 2.5 cm. in diameter. Studies of the microscopic sections revealed tissue with the same characteristics as the original adenocarcinoma of the rectum (fig. 4). At the time of discharge the serum nonprotein nitrogen was 41 mg. per cent. He was placed on gantrisin therapy for a urinary infection with A. aerogenes. At the time of his first postoperative visit, 2 weeks later, the urine was microscopically normal and he voided satisfactorily. Up until the present time he has been free from urinary infection and has had no symptoms of recurrent tumor (fig. 5).

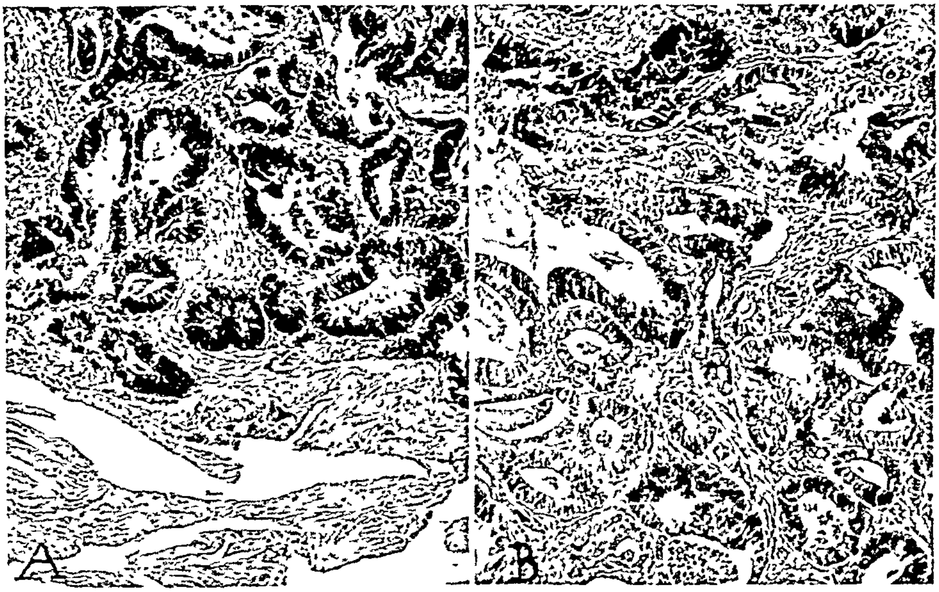

FIG. 4. Sections from tumor tissue removed at time of radical amputation of penis. *A*, mass of adenocarcinoma within spongy tissue of corpus cavernosum; B, metastatic adenocarcinoma in right crus of penis.

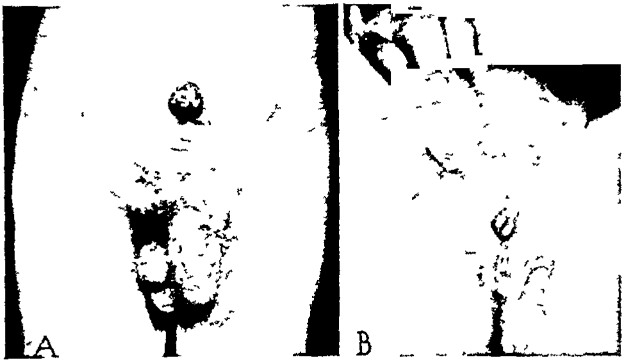

FIG. 5 Photograph following radical amputation of penis. *A*, note colostomy opening and scrotal hernia; *B*, slightly protruding transplanted urethral orifice with no tendency toward stricture formation.

DISCUSSION

The pertinent clinical data from the cases previously published and the one herein reported are condensed in table 1. It should be noted that the primary tumors were all low rectal lesions. In four of the cases the tumor mass was described as palpable on digital rectal examination. Of the 2 remaining cases, one lesion was described as being 6 cm. inside the rectum on proctoscopic examination, while the tumor location in the other case is assumed to be low because of the trans-sacral surgical approach. The primary rectal lesion was operable in 3 cases; an abdominoperineal resection having been carried out in two and a trans-sacral rectal amputation in the third. The other 3 cases were seen in the terminal stage of the disease and were considered inoperable because of the poor general condition of the patient due to marked local extension of the growth or distant metastases. In the case presented by Thompson the first symptoms were those due to the penile metastasis while all the other cases had bowel symptoms for varying periods of time before the metastatic penile lesions occurred. The long interval which elapsed between treatment of the primary lesion and the appearance of the metastatic disease was of interest in 2 cases. The patient presented by Cattell and Mace did not have symptoms of metastatic adenocarcinoma of the penis for 30 months after abdominoperineal resection while our patient did not show clinical manifestations of penile metastasis for 60 months following rectal surgery.

Priapism was present in three of the reported cases. Although this condition is commonly seen in primary tumors of the penis, the incidence is greater in metastatic lesions. According to Stein and Hantsch the priapsim is due not only to tumor replacement of the cavernous bodies but also to secondary stasis and thrombosis of blood sinuses not directly involved. Niewiesch emphasized that, in spite of its rare occurrence, the possibility of metastatic tumor of the penis should be considered whenever priapism is seen. Urinary retention, due to encroachment of the tumor mass upon the urethra, was the presenting urinary symptom in 2 cases. Our case is the only one to have neither of the above symptoms; the genito-urinary symptoms having been perineal pain and painful nodules in the penis.

Surgical treatment of the metastatic penile lesion was carried out in only 3 cases. In the case reported by Niewiesch the lesion was treated by simple amputation of the penis at the base. Six months later the patient had multiple metastases, among which was a destructive tumor under the symphysis near the urethral opening. The patient reported by Cattell and Mace had an isolated metastatic mass in the left corpus cavernosum near the penoscrotal junction, the mass measuring 5 by 2.5 cm. The lesion was removed by local excision. Treatment in our case consisted of local excision of an isolated metastatic mass 5 years after primary rectal surgery, followed by radical amputation of the penis 10 months later for metastases within the right corpus cavernosum.

Three of the reported cases were in the terminal stage of the disease when first seen and were all deceased within 5 months following the appearance of the penile lesion. The patient reported by Niewiesch died within 10 months from

TABLE 1. *Pertinent clinical data from the case presented and those collected from the literature*

UTHOR	AGE OF PATIENT	LOCATION OF RECTAL LESION	OPERABILITY OF RECTAL LESION	TIME OF OCCURRENCE OF PENILE LESION	GENITO-URINARY SYMPTOMS	TREATMENT OF PENILE LESION	SURVIVAL OF PATIENT
iesch, 1933	69	Location not stated. Probably low lesion because of trans-sacral surgical approach	Trans-sacral rectal amputation	18 months after trans-sacral rectal amputation	Priapism	Simple amputation	10 months after amputat of penis
esan, 1935	72	Low in rectum. Palpable on digital examination	Inoperable. Inguinal glands involved. Colostomy done	3 months after colostomy	Urinary retention	None	5 months
and ntsch, 1937	62	Described as 6 cm. inside rectum on proctoscopic examination	Inoperable	2 months after onset of bowel symptoms	Priapism and painful nodules in penis	Treated with x-ray therapy. No change in condition	4½ months
npson, 1950	70	At the level of prostate gland. Palpable	Inoperable	Presenting symptoms were those due to penile metastasis	Retention of urine	None	4½ months
ll and ace, 1951	30	Left lateral rectal wall. Palpable	Abdominoperineal resection. No glands or local extension	30 months after abdominoperineal resection	Priapism with pain	Local excision 5 x 2.5 cm. mass from left corpus cavernosum and part of rt. corpus cavernosum	Alive 9 years after exci of metastasis
l, 1952	54	Above the prostate on posterior wall of rectum. Palpable	Abdominoperineal resection. Metastasis found in one regional gland	60 months after abdominoperineal resection	Pain in perineum Feb. 1951. Painful nodules in penis Oct. 1951.	Local excision of mass in ischiocavernosus muscle 3-9-51. Radical amputation of penis 1-2-54	Alive 6 years after abdom perineal resection. Aliv months after first pe metastasis

generalized metastases. Our case and that presented by Cattell and Mace are especially interesting from the standpoint of survival. A long time interval elapsed in each instance, following the abdominoperineal resection, before the metastatic penile lesion appeared. In one instance the patient was alive and well 9 years after excision of the metastasis while in the other the patient is alive and well 6 years following the abdominoperineal resection and 18 months after the occurrence of the metastatic penile lesion.

The occurrence of metastasis in the corpus spongiosum of the urethra was noted in only 2 cases. The case described by Stein and Hantsch had no postmortem examination but definite nodules were present in the glans penis. Biopsy of other nodules in the shaft of the penis showed typical metastatic adenocarcinoma from the rectum. The case studied by Thompson showed a metastatic nodule in the glans penis which was biopsied, and autopsy revealed extensive involvement of the corpus spongiosum as well as the corpora cavernosa.

The metastatic route taken by cancer cells from primary adenocarcinoma of the rectum to the penis is not known. Stein and Hantsch explain the extension as being along the pathway of least resistance, namely into the ischiorectal fossa, then through the junction of the deep and superficial triangular ligaments with Colles' fascia into the superficial perineal space. They also assert that, since cancer cells do not usually spread against fascial planes, metastatic involvement of the corpus spongiosum would probably result from extension through the urogenital diaphragm.

We believe that there is a more logical explanation to account for the occasional spread of adenocarcinoma of the rectum to the penis. According to Callander, the rectal veins form a rich hemorrhoidal plexus within the bowel wall. The superior hemorrhoidal vein drains into the portal system and the middle and inferior hemorrhoidal veins drain into the inferior vena cava. Since the venous drainage of the rectum is away from the penis, one would not expect venous metastases to the penis from primary rectal growths. Some of the rectal lymphatics drain to nodes lying along the superior hemorrhoidal veins and then to the nodes of the mesentery while other lymphatic channels follow the middle hemorrhoidal vessels and empty into the hypogastric lymph nodes. Most of the inferior hemorrhoidal lymphatics, however, pass through the perineal region, later to join the inguinal glands. Many of the lymphatics in the perineal region follow the course of the inferior hemorrhoidal vein and internal pudenal vein from which it branches. Since the internal pudenal vessels not only give rise to the inferior hemorrhoidal vessels but also supply the penis and ischiocavernosus muscles, one might well expect a spread through lymphatic channels to these structures. According to Miles, carcinoma of the rectum may extend through lymphatic channels downward into the wall of the bowel below the growth, into the rectal sphincter and ischiorectal fossa. It may be assumed that cancer cells gain entrance to the peri-anal lymphatics by this means or by contamination of the anal area with cancer cells at the time of the abdominoperineal surgery. It would seem to us that the above mentioned pathway is the most logical explanation for the occurrence of an isolated metastasis in the penis, secondary to adenocarcinoma of the rectum.

SUMMARY

Metastatic carcinoma of the penis secondary to carcinoma of the rectum is rare, there being but 5 authentic cases reported in the literature.

A sixth case has been presented, the literature reviewed and the pertinent clinical data discussed.

ADDENDUM

Since this manuscript was submitted, Bowersox and Frerichs (J. Urol., **68:** 897–902, 1952) have reported a case of adenocarcinoma of the colon with secondary tumor of the penis. Our case, therefore, is the seventh published case of this sort.

277 Alexander St., Rochester, N. Y.

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CAUSES OF DEATH IN UROLOGICAL PRACTICE AS STUDIED CLINICALLY AND ON A HUNDRED AUTOPSIES

VITTORIO GIONGO AND UMBERTO MUSIANI

From the Clinica Chirurgica of the University of Bologna, Italy

The object of this paper is not the study of the inner mechanism of death as such, but the research into the peculiar anatomical and functional alterations leading to it. To achieve this end we have deemed necessary to take into consideration not only clinical data, but also postmortem findings, the possibility of wide discrepancies between clinical objectivity and the pathologists' statement being well known.

We have therefore considered only those patients who died during their stay in the hospital, and upon whom autopsies were performed (100 autopsies on 133 casualties or 75.2 per cent).

By means of a careful scrutiny of clinical and postmortem data, we have attempted to define the principal cause of death and the conditions leading to it, in order to reconstruct the morbid progression resulting in death.

References on the subject are rather scarce, while papers on every single ailment are so abundant that it is practically impossible to quote them integrally. As far as we know, Hyman and Mencher (J. Urol. **33:** 315, 1935) and MacKenzie and Seng (J. Urol. **29:** 321, 1933) have published papers on causes of death in urological patients, but, as the structure of our study is substantially different, we restrict ourselves to this acknowledgment.

To classify our subject matter as rationally as possible, we have schematically presented the fatal pathological conditions with their various complications clearly outlined: Deaths caused by 1) fatal conditions extraneous to the primary disease, 8 cases; 2) normal evolution of the disease, 24 cases; 3) inflammatory complications, 47 cases; 4) noninflammatory conditions associated with interventions or with the use of instruments, 21 cases.

As shown in this scheme, the causes of death are divided under various heads, each of which will be singly analyzed. Practical deductions will then follow.

FATAL CONDITIONS EXTRANEOUS TO THE PRIMARY DISEASE

Under this head we have classified fatal conditions not strictly to be ascribed to the original genito-urinary disease which brought the patient to the hospital; such conditions do not necessarily represent complications. They include diffuse arteriosclerosis, 1 case; cerebral hemorrhage, 1 case; cardiac failure, 6 cases; causes of death having no apparent relation to the primary disease.

The case of a patient whose death, 21 days after operation, was caused by diffuse arteriosclerosis deserves particular notice. This 85 year old man, on the eleventh day after a Freyer prostatectomy, with an already healed cystostomy wound, and urethral miction reinstated, began to show signs of mental confusion and rapid decline. Autopsy findings revealed general arteriosclerosis most evident in the brain and kidneys.

Cerebral hemorrhage was responsible for the death of a 60 year old patient, 4 days after cystostomy. He suffered from diabetes, but his age and blood pressure, still within normal limits, gave no hint of a possible fatal termination.

Among cardiac causes of death, coronary infarction was observed twice. (Both patients were taking estrogens for prostatic carcinoma; one carried an indwelling catheter; the other died 20 days after orchiectomy.) Acute heart failure was observed 4 times (three of the patients operated respectively of Freyer prostatectomy, cystostomy, and explorative laparotomy for retrovesical tumor). No connection could be traced between the operations and the heart failure. Autopsy findings showing grave degenerative lesions involving the aorta confirmed the diagnosis as in the previous cases of infarct. The fourth patient of this group was a man affected with syphilis and diabetes; he was hospitalized for stenosis and peri-urethral abscess; no operative intervention took place. He died 52 days later, when the urinary conditions had very much improved. Autopsy findings showing coronary sclerosis, myocardosis and luetic aortitis gave abundant reason for a fatality, but a gastric carcinoma, with hepatic and pulmonary metastases, whose course had been wholly asymptomatic, was also present.

The aforementioned deaths, amounting to the 8 per cent of our statistics, represent the normal output of an urological service, mostly composed of elderly people, already tried by a long illness. Such fatalities are not easily predictable, as patients come to the urologist with an already taxed functional balance, which, despite favorable clinical findings, can be easily upset.

DEATHS CAUSED BY NORMAL EVOLUTION OF DISEASES OF THE UROGENITAL TRACT

In this second group we have assembled the fatal conditions resulting from the normal evolution of a disease free from complications and left more or less to itself. Such conditions include the cancerous cachexy originating from diffuse metastases, 12 cases; tuberculous generalization, 1 case; acute anemia subsequent to profuse hemorrhage of easily bleeding lesions, such as papilloma and vesical varices, 2 cases; lastly uremia caused either by the extensive destruction of renal parenchyma, or by ureteral occlusion by calculi or neoplasic infiltration, 9 cases.

In the 12 patients victims of malignant cachexy, autopsy findings revealed metastatic diffusions incompatible with life. Ulcerated hepatic metastases of a carcinoma of the testis had caused an hemoperitoneum. In another case, a carcinoma of the bladder had given metastases in the corpora cavernosa of the penis. This infrequent localization, described elsewhere by one of us, had led, intra vitam, to doubts as to the existence of an induratio penis plastica. In two cases of prostatic cancer the liver was literally crammed with metastases, and in 1 case this organ tipped the scales at kg. 8,5. Tuberculous generalization caused the death of a 54 year old female patient, 69 days after the removal of a ureteral stump which had caused a lumbar fistula following a nephrectomy. Autopsy findings showed diffuse tuberculosis, with evident localization in the meninges and peritoneum. Two patients died of hemorrhage: one, an 85 year old male patient, suffering from a benign papilloma had reached a nearly terminal condition through his own negligence when brought to us; the other died 5 days after an epicystotomy performed for calculosis. An uncontrollable hemorrhage, showed by autopsy to proceed from ulcerated vesical varices, was the cause of this death. In 9 patients in whom morbid processes were allowed to progress untouched, death was brought about by uremia. In 5 cases extensive destruction of renal parenchyma due to tuberculosis, 3 cases; polycystic disease of kidneys, 1 case; and sclerotic kidney, 1 case; was responsible for the exitus. The lesions revealed by autopsy were such as to render the still functioning renal parenchyma almost unrecognizable, demonstrating thus the capacity of the organism to withstand an inconceivable degree of destruction in such an important emunctory organ. In 3 cases uremia was caused by neoplasic infiltration of both ureters from a carcinoma of the uterus, 1 case; and of the bladder, 2 cases. The conditions of these patients were so desperate that a nephrostomy was considered inadvisable. Uremia, consequent to renal occlusion by a calculus wedged in the right ureter, was responsible for the death of a 31 year old female patient suffering from calculous left hydronephrosis. Catheterization of the ureters, pushed above the calculi, failed to bring relief, and only after 6 days of anuria the patient passed 150 cc of urine, and the following day 500 cc. Uremia progressed nevertheless to coma and death, which took place on the tenth day, with a nonprotein nitrogen of 6.97. Degeneration of glandular tissue, chiefly renal and hepatic, was revealed at autopsy. The last mentioned localization explained the presence of jaundice during the first days of anuria, which subsided later on. This report seems to be of particular interest, as it shows how lesions resulting from renal occlusion, in conjunction with hepatic disturbances, become very soon irreparable, and lead to a fatal termination, even when there is some functional renal recovery.

The causes of death examined in this group are generally unavoidable as they represent the terminal stage of a fatally evolving illness. Only acute anemia could be prevented, and, perhaps, considering the progress of antibiotic and chemical therapy, tuberculous generalization.

FATAL INFLAMMATORY COMPLICATIONS

Inflammatory complications of a fatal nature are extremely frequent in diseases of the urogenital tract, and represent one of the principal causes of death. Death may occur through a) toxicosis, when the process remains relatively localized; b) direct infection, as when a perirenal purulency opens directly into the peritoneum; c) through hematogenous dissemination with septic pyemia; d) through the mechanism of ascending pyelonephritis. The last instance is the commonest. In our analysis of mortal inflammatory involvements we will then consider these 4 cases. It is generally known that inflammatory conditions often arise during the course of such diseases as vesical carcinoma and vesical calculosis, so as to be considered a normal evolution of the disease. On the other hand, it is admitted that instrumentation and surgical intervention are often responsible for promoting infection, in spite of careful precautions and the use of antibiotics: While not abscribing to instrumentation and surgical intervention a direct influence upon infection, we prefer to consider separately patients who died through inflammatory complications without having been submitted to instrumentation or operation.

The 47 casualties due to inflammatory complications are divided as follows: without instrumentation or operation, 7 cases; after instrumentation, 14 cases; after surgical intervention, 26 cases..

The foregoing data have a purely chronological value in that the deaths occurred after but not because of the treatment mentioned. Cases in which a relationship between the treatment used and the fatal inflammatory complications could be clearly established will be further and separately discussed.

We will now analyze seven casualties, for which instrumentation or surgical interventions could not be held responsible. In 1 case the mechanism of fatal infection was rather unusual: In a 70 year old female patient a right pyonephrosis determined a purulent perinephritis. The ensuing perforation of the peritoneum ended in a rapidly fatal peritonitis. In 2 cases the infection spread through hematogenous dissemination: an aposthematous nephritis characterized by the presence of numerous small cortical abscesses was observed at autopsy. In the first of these 2 cases the primary cause of infection was a putrid cystitis following prostatic cancer; in the second one a prostatic abscess opening into the urethra had determined the fatal pyemia. Four patients were victims of uremia determined by ascending pyelonephritis originated from vesical carcinoma (3 cases) and calculous cystitis (1 case). In this last instance infection was fostered by the co-existence of renal calculosis. Autopsy reports of these 4 patients showed the typical *rein des urinaires* with the characteristic lesions of ascending infection. The seven above mentioned casualties observed purely from a pathologist's viewpoint show that inflammatory complications can bring about a fatality through various processes.

Instrumentation was followed by 14 casualties: in 13 cases after urethral catheterization or the use of indwelling catheter, in 1 case after the use of metallic ureteral sound.

In 5 patients the indwelling catheter had determined a peri-urethral phlegmon. In 3 cases (2 adenoma and 1 prostatic cancer) autopsy made clear that infection had spread to the bladder and death had occurred through ascending pyelonephritis. In the fourth patient of this group (sclerosis of bladder neck) infection had been carried by hematic diffusion and determined an aposthematous nephritis. The exitus in the fifth case (prostatic adenoma) was caused by a toxicosis: autopsy showed a fatty and hyalin degeneration of the kidney, with no symptoms of diffusion from the primary urethral focus. In 7 patients the primitive focus was represented by cystitis; in 4 cases the already mentioned processes of ascending pyelonephritis caused the fatalities; in the other two instances the patients were carrying an indwelling catheter for relief of prostatic obstruction: diffusion of infection to the bladder by way of the blood stream determined in 1 case an aposthematous nephritis, and in the other bronchial pneumonia, with confluent foci, of evident metastatic origin. In the seventh patient the use of catheter was followed by severe cystitis, ending fatally in spite of intense antibiotic therapy. Autopsy showed a toxic nephrosis.

From what has been said thus far, it appears that in 5 cases the infection which later proved fatal began in the urethra, often following catheterization prior to admission. Such instrumentations were generally performed by inexperienced persons and without the indispensable antiseptic precautions. In the other 7 cases, however, infection appeared in the bladder in spite of the most careful handling. As for timing the onset of infection, we have not been able to trace a direct connection between the duration of drainage and the appearance of infection. A peculiar process of direct infection was observed in a patient suffering from carcinoma of the fundus of the bladder in which a decubitus caused in neoplastic tissue by a Tiemann indwelling catheter determined a *perforation of the bladder* into the peritoneum and a fatal issue within a few hours. An unsuccessful attempt to remove endoscopically a wedged right ureteral calculus by means of a metallic sound was another cause of fatality. A violent *sepsis* followed on the second day, and on the third death intervened, in spite of intense antibiotic and sulfonamide treatment. Aposthematous nephritis revealed by autopsy showed the localization of the septic pyemia in the injured organ. The extreme risk always inherent in unsuccessful attempts to dislodge a stone endoscopically is once more made evident by the results of this case.

In 26 patients clinical data and autopsy reports have established the existence of fatal inflammatory complications after surgical intervention. The lapse of time intercurring between intervention and death was variable.

Among these postoperative casualties 1 death occurred 3 days after cystostomy through ascending pyelonephritis, and another one for the same reason 163 days afterwards: the patient on whom the surgical repair of urethra had been performed died 7 months after the last operation.

We will now consider fatal inflammatory complications which occurred after but not through intervention. In the aforementioned group ascending pyelonephritis is responsible for twelve out of fourteen casualties through inflammatory complications following cystotomy, while one fatality must be traced to infection of the surgical wound and another to metastatic bronchial pneumonia determined by hematogenous diffusion (on the thirteenth postoperative day). The remarkable prevalence of ascending diffusion would lead to believe that cystostomy fostered this particular mode of infection. However, looking more closely into the conditions that brought the patients to surgical intervention, we find 3 cases of vesical carcinoma, 3 of prostatic carcinoma, 2 of infected vesical calculosis, 1 urethral stenosis with prostatic calculosis. In 9 cases out of twelve the infection was already present, and the fatal evolution possible and even probable, without cystostomy. The other 3 patients, all of them suffering from prostatic adenoma, were in very poor conditions: the first, 70 years old, died on the eighty-second postoperative day; he suffered from vesical calculosis, and for this reason had undergone 3 operations in 7 years' time. Autopsy findings showed too a right hypernephroma whose course had been wholly asymptomatic. The second patient, 64 years old, was carried away by uremia on the fourteenth postoperative day: autopsy findings revealed the presence of a sclerotic and pyelonephritic left kidney in addition to the ascending right hemorrhagic pyelonephritis. As for the third patient, 68 years old, he died 3 days after aeruginosa), but the structure and disposition of the urinary tract helps us to understand how these germs can find there an ideal growing medium. As yet, we do not possess a drug capable of determining and insuring the complete and safe sterility of the urinary tract.

FATAL CONDITIONS ASSOCIATED WITH INTERVENTION OR INSTRUMENTATION

Even admitting that in some cases mortal infection might have been fostered by interventions such as cystostomy and Freyer prostatectomy, still intervention cannot be held responsible for such complications in the majority of cases. However this connection can be directly traced in those cases of infections of the surgical wound, such as in the cases of cystostomized patients in whom pericystitis developed, and in the two nephrectomized patients, when infection of the perinephrium was followed by peritonitis. As for instrumentation, there is no doubt that in lethal cases originating from peri-urethral phlegmon (and ensuing complications) catheterization was the primary cause; and that instrumentation was also directly responsible for the fatal sepsis which followed the use of a metallic sound.

Having largely examined the inflammatory complications originating from intervention or instrumentation, which have been so far grouped with the other cases for the sake of schematization, we will now observe those non-inflammatory fatal conditions arisen from surgical intervention or instrumentation, or in which we at least presume to trace a connection between operation and fatality.

Among the deaths connected to instrumentation, besides the instance of fatal sepsis following ureteral catheterization with a metallic sound another case deserves particular notice. In a 60 year old man, right ascending pyelography (performed elsewhere) showed a neoplasm of the lower renal pole and hydronephrosis; the patient went home, but anuria set in and 3 days later he was admitted to our clinic. Diuresis could not be re-established even by anesthetic infiltration of the renal pedicles, and exitus took place on the sixth hospital day, being the fourth day of anuria. Autopsy confirmed the previously made diagnosis of right renal tumor and hydronephrosis, but showed as well an important left hydronephrosis caused by a marked ureteral stenosis. Once more the inopportunity of performing an ascending pyelography in a certainly diseased kidney without having any knowledge of the functionality of the other one, and, which is even worse, knowing that the diseased kidney is the functioning one of the two, is clearly illustrated. The stimulus exercised by the pyelography can easily determine in an already compromised organ, an irreversible renal inhibition.

Non-inflammatory complications connected with surgical intervention were the cause of death in 20 patients: Three patients died of surgical shock a few hours after intervention. They were affected with renal tumor; in 1 case the operative act was limited to an explorative lombotomy, as the voluminous cancerous mass could not be extirpated. In the other 2 instances papillomatosis of the renal pelvis was found, one in a horseshoe kidney. Exitus took place respectively on the twelfth, eighteenth and thirtieth postoperative hour. The state of shock in these 3 cases was so severe that even infusion therapy was of no avail.

Autopsy showed no lesions to which the fatal condition could be ascribed, therefore the diagnosis of shock appeared the only one possible. The recurrence of fatal shock in interventions for renal tumors is not to be wondered at, as it is a well known occurrence.

At a greater interval after intervention, respectively after 48 and 72 hours, 2 patients, on whom Freyer prostatectomy had been performed, (1 cancer, 1 adenoma), died of cardiovascular collapse. In the former case, autopsy showed acute dilatation of the heart; in the latter, a diffuse myocardiosclerosis. Preoperative general conditions of both patients gave no reason to fear a fatal outcome.

Postoperative hemorrhage was responsible for three casualties. The first case was submitted to partial nephrotomy for calculosis; exitus took place suddenly on the thirty-sixth postoperative hour. A large retroperitoneal hematoma was observed at autopsy, while no more blood than is usual in similar cases had come through the drainage tube. A secondary hemorrhage carried away the second patient 12 days after a resection of the upper renal pole for calculosis. The third patient died 12 hours after a Freyer prostatectomy for adenoma. Postmortem examination showed the entire excretory system to be full of blood, which had invaded the bladder, the ureters and the renal pelvis. Death through postoperative acute anemia is today to be considered a quite exceptional occurrence; however this should not make us forget the fact that there are cases in which it is almost impossible to stop a hemorrhage, even disposing of all the direct and indirect therapies now in use. We must also remark that in the above mentioned cases, routine blood tests did not raise any apprehension before operation.

Embolism caused the death of 7 patients. In the three cystostomized patients for prostatic adenoma the embolus was localized in the pulmonary artery; intense cyanosis and dyspnea set in, in 1 case 4 days, and in the other two, 7 days after operations, dramatically striking down patients apparently in good condition. The diagnosis made *intra vitam* was confirmed at autopsy, and in 2 cases the reports clearly showed a thrombosis of the perivesical plexus, the presumable starting point of the fatal embolus. These facts point to the advisability of avoiding any traumatism of the venous vesical plexus while performing a cystostomy as it may lead to dangerous thrombosis.

A 61 year old patient, who died 6 days after a nephrectomy for tumor, presented a singular complication. His general condition was poor; postmortem examination, beside metastases in the lumbo-aortic lymph glands and the liver, showed a thrombosis localized in the iliac artery, which [illegible] [illegible] considered the primary cause of death.

The acute gastric and duodenal ulcers which, through [illegible] [illegible] brought patients to death, can be connected in all probability [illegible] [illegible] In the first case, the patient, a 67 year old man, who underwent [illegible] tomy 25 days previously, was a confirmed drinker, and this [illegible] for the greater fragility of the mucous membrane; while in [illegible] year old male nephrectomized 16 days before for hydrone[illegible] [illegible] bolus could explain the large and recent gastric ulcer, in [illegible] the gaping end of a small artery was observed. None of the patients in the past had suffered from gastric disturbances; the melena appeared respectively in the seventeenth and in the thirteenth postoperative day. If in these 2 cases the embolic origin of the ulcers appears almost certain, the same cannot be claimed for the third patient. This 56 year old man died through hematemesis and melena 6 days after being cystostomized for adenoma. At autopsy the blood was found to come from a completely asymptomatic ulcer implanted on the scar of a gastro-enterostomosis performed 9 years previously. Pathogenesis of this case appears much more uncertain than in the previous 2 cases, as the ulcer did not present the signs of recentness observed in the previously mentioned 2 cases, which constituted the proof of the embolic origin. It is probable that postoperative humoral alterations (acidosis?) may have reawakened the old morbid process. At any rate, melena and hematemesis from acute and hitherto asymptomatic ulcers, known to the old school of pathologists, represent now an exceptional occurrence.

Two nephrectomized patients died through insufficiency of the remaining kidney. In the first case our patient was a 33 year old man, on whom, 6 years previously, a right hypocondriac marsupialization of a vast pyonephrotic collection, erroneously diagnosed as a pancreatic cyst, had been performed. Preoperative examination revealed a moderate functional capacity of the left kidney; a nephrectomy *par morcellement* of the right kidney was therefore undertaken. The patient showed grave symptoms of uremia, and died on the fourteenth postoperative day. Diffuse amyloidosis also present in the nonoperated kidney, evidently with a precarious functional balance, and therefore unable to withstand the stress of an intervention, was made evident at autopsy. The other 55 year old male patient suffered from colic determined by a right calculous hydronephrosis. On the left side the cavities were equally enlarged, but the function of the left kidney was satisfactory, as the intravenously injected dye appeared on this side after 5 minutes. It should also be mentioned that 1 year previously the patient had been operated on for postoperative peptic ulcer, while in a state of marked anemia, and the renal intervention was performed on his express and insistent request, since, he claimed, the constant pain was unbearable. After intervention anuria set in, and exitus in a state of coma took place on the third postoperative day. Autopsy showed hydronephrosis of the remaining kidney, with hyalin degeneration of the parenchyma.

Before the common use of antibiotics, 3 patients died of *postoperative* bronchial pneumonia. The three of them had been cystostomized, two for adenoma, and the other one for stenosis. Death happened respectively on the eighth, twenty-first, and third postoperative day, and in the 3 cases the complication appeared during the winter. Although the 3 patients were probably predisposed and hardly put up any resistence, we firmly believe that penicillin and streptomycin would have given them a fair chance of pulling through. Since the introduction of antibiotics we have not lost a patient through postoperative bronchial pneumonia. Only pneumonias originated by the migration of mycotic emboli from the inflammatory foci in the surgical wound are sometimes mortal.

This last group, including deaths connected with surgical intervention or instrumentation, is worthy of a few general remarks. Although the infusion therapy has minimized the danger from operative shock the removal—or even the bare attempt to remove—a renal tumor, still takes a heavy toll in fatalities. This is a fact, well known to all surgeons. Even to-day it is not always possible to stop every hemorrhage, and this comparatively rare occurrence represents a justly feared complication. In 4 patients embolism was a positive and direct cause of death, and in three other cases it had also to be taken into account, through the little known processes of gastric and duodenal ulcer. As regards primitive postoperative bronchial pneumonia, our actual therapeutic possibilities allow us to care for this occurrence with a wide margin of safety. When we consider the remaining causes of death (cardiac collapse, insufficiency of the remaining kidney) we are bound to recognize that our preoperative functional examinations are only relatively reliable; while measuring the actual functional capacities of the organ, they do not, however, give a trustworthy account of its power of resistance, especially when the organ in question is already on a precarious functional balance.

SUMMARY

In a period of 12 years, 133 patients died in the Urological Section of the Clinica Chirurgica in the University of Bologna. One hundred of them were brought to autopsy (75.2 per cent). Experience shows that postmortem examinations point out clinically unsuspected lesions which nevertheless are essential in determining the fatality. So we have on purpose set aside the 33 patients not submitted to autopsy, while we have tried to determine with the greatest accuracy the cause of the remaining 100 deaths, taking into account clinical data obtained at the moment of admission, during the progress of illness and postmortem data. Our ultimate aim has been to collect the greatest number of facts throwing light on fatal conditions and complications.

We have divided our observations in 4 large groups. In the first we have gathered all fatal conditions having no apparent connection with the urological disease, such as diffuse arteriosclerosis, cerebral hemorrhage, myocardic infarction, and acute heart failure. The aforementioned causes induced by the age of patients and the chronic progress of the primary disease, claimed 8 patients out of a hundred. The second group included deaths representing the normal evolution of a disease left to itself, such as malignant cachexia, tuberculous generalization, acute anemia caused by papilloma or vesical varices, and, lastly, uremia, following destruction of the renal parenchyma by tuberculosis, polycystic disease of the kidneys, sclerotic pyelonephritic kidney, neoplastic infiltration of ureters, and renal inhibition through calculosis. Twenty-four patients succumbed to the aforementioned conditions, no one of them preventable with the exception of the hemorrhage. Inflammatory complications are the commonest cause of death, and are grouped under the third heading. They claim 47 out of one hundred patients, showing thereby the pre-eminence of infection in Urology. Of these 47 patients, 30 died through ascending pyelonephritis (64 per cent), 8 through hematogenous diffusion (17 per cent), and 3 through infection of the wound (6.4 per cent). It could be established with a certain accuracy that in

32 cases (66 per cent), the infection originated in the bladder, and spread from there. In the fourth group we included all conditions that seemed connected with surgical intervention or instrumentation. Besides the infection of the surgical wound (observed in the preceding group), we have here analyzed conditions of shock and postoperative collapse, of postoperative bronchial pneumonia, hemorrhage, embolism, and insufficiency of the remaining kidney. Twenty deaths are ascribed to this group, and in all of them the cause of death has been made evident and analyzed.

CONCLUSIONS

In urological patients, as a complication of the primary disease or connected with surgical intervention or with instrumentation, infection is the commonest cause of death. The propagation of infection is fostered by the peculiar structure of the urogenital tract; in most cases the bladder is to be considered the starting point. A considerable number of patients however were either victims of the fatal evolution of the primary disease or succumbed to other causes connected with age or associated pathological changes, and were beyond our aid. In 20 cases the fatal condition seemed to be directly connected with surgical intervention, and death was often due to functional insufficiency of the remaining kidney. Some peculiar (and often dangerous) complications are associated with determined surgical interventions, such as shock after operation for renal malignancy, embolus of the pulmonary artery due to thrombosis of the perivesical plexus in cystostomized patients, or hemorrhage following nephrectomy or partial nephrectomy.

Were any of these fatalities preventable? We would call preventable all the casualties due to negligence of the patient himself, as in renal inhibition from calculosis, and acute anemia from papilloma. Results would have been very different if the patients had asked for medical help before their condition had become critical. Death from vesical hemorrhage due to varices occurred because the lesion was unsuspected. Complications considered fatal only a few years ago, such as postoperative pneumonia, infection of wound or general tuberculosis are now easily controlled, thanks to the progress of antibiotic and chemical therapy.

Aiming to lower even further the percentage of mortality, how should we determine the trend of future research? A comprehensive answer cannot of course be given; however two objectives seem to us of peculiar interest: 1) The functional examinations at our disposal at present do not as a rule give us a precise hint as to the possibility of future complications. Every effort aiming to obtain an exact evaluation of the functioning capacity would determine a decrease in the number of casualties. 2) In an important number of cases the bladder was the primary seat of the later fatal infection. It is beyond actual possibilities to sterilize and to keep the bladder in an aseptic condition. If in the future this achievement should become possible, the prognosis in urological diseases would be considerably less severe.

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PLASMACYTOMA (MULTIPLE MYELOMA) OF TESTIS: A REPORT OF FOUR CASES AND REVIEW OF THE LITERATURE

MEYER M. MELICOW AND GEORGE F. CAHILL

From the Squier Urological Clinic and Presbyterian Hospital, Columbia University, College of Physicians and Surgeons, New York, N. Y.

The vagaries of metastatic malignancy are manifold and interesting. The diffuse spread in patients who are in the terminal stages of cancer is not remarkable but early or lone involvement of an area distant and apparently unrelated to the primary site often presents a puzzling clinical picture. The pathological report then comes as a surprise, but at the same time clarifies and explains the unusual findings. Plasmacytoma (multiple myeloma), a malignancy that arises in bone marrow, is apt to follow such a course. We present two patients in whom the testicular involvement was the only evidence—at time of operation—of metastatic spread from the primary focus. In one patient (fig. 1) the tumor apparently arose in the right tibia while in the other (fig. 2) the diagnosis of multiple myeloma was based on characteristic findings in the contents of a sternal puncture. In two other cases the metastasis to the testis was part of a diffuse process and was discovered at autopsy. We believe that the 2 patients in whom a diagnosis of plasmacytoma of the testis was made from operative specimens, are the first to be so reported. All previous reports were based on autopsy findings. In 1927 Kirshbaum[1] reviewed the literature on the subject of multiple myeloma involving the testis and cited 4 cases, including one of his own. The first was an autopsy report by Ghon and Roman[2] on a 72-year old man with scattered myeloma cells in one testis (right) but no real tumor. The second case was mentioned by Porchownik[3] in 1931 and was of a bilateral testicular involvement, also found at autopsy. Porchownik did not see the case but stated that it had been presented at the Kiev Therapeutic Society by Weizberg in 1930. The third report was by Ulrich.[4] The patient, a 55 year old man, had a left orchiectomy for tumor. Several small nodules containing plasma cells were found but the diagnosis was in doubt because there were no demonstrable osseous changes. At autopsy, however, diffuse multiple myeloma of the bones was found. The lower third of the right testis contained a greyish yellow tumor which too was composed of plasma cells. Ulrich stated, that in the reviews of multiple myeloma made by Wallgren in 1920,[5] Geschickter and Copeland in 1928[6] and Magnus-Levy in 1932,[7] no mention was made of

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[4] Ulrich, H.: Multiple myeloma. Arch. Int. Med., **64**: 994, 1939.

[5] Wallgren, A.: Untersuchungen uber die Myelomkrankheit. Upsala Lakaref. Forh., 113, 1920.

[6] Geschickter, C. F. and Copeland, M. D.: Multiple myeloma. Arch. Surg., **16**: 807, 1928.

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metastatic spread to the testis. Kirschbaum's patient, the fourth case, was a 62-year old man who suffered from pain in the back of his neck and chest, frequency of urination and dyspnea. The scrotum was not examined. The patient

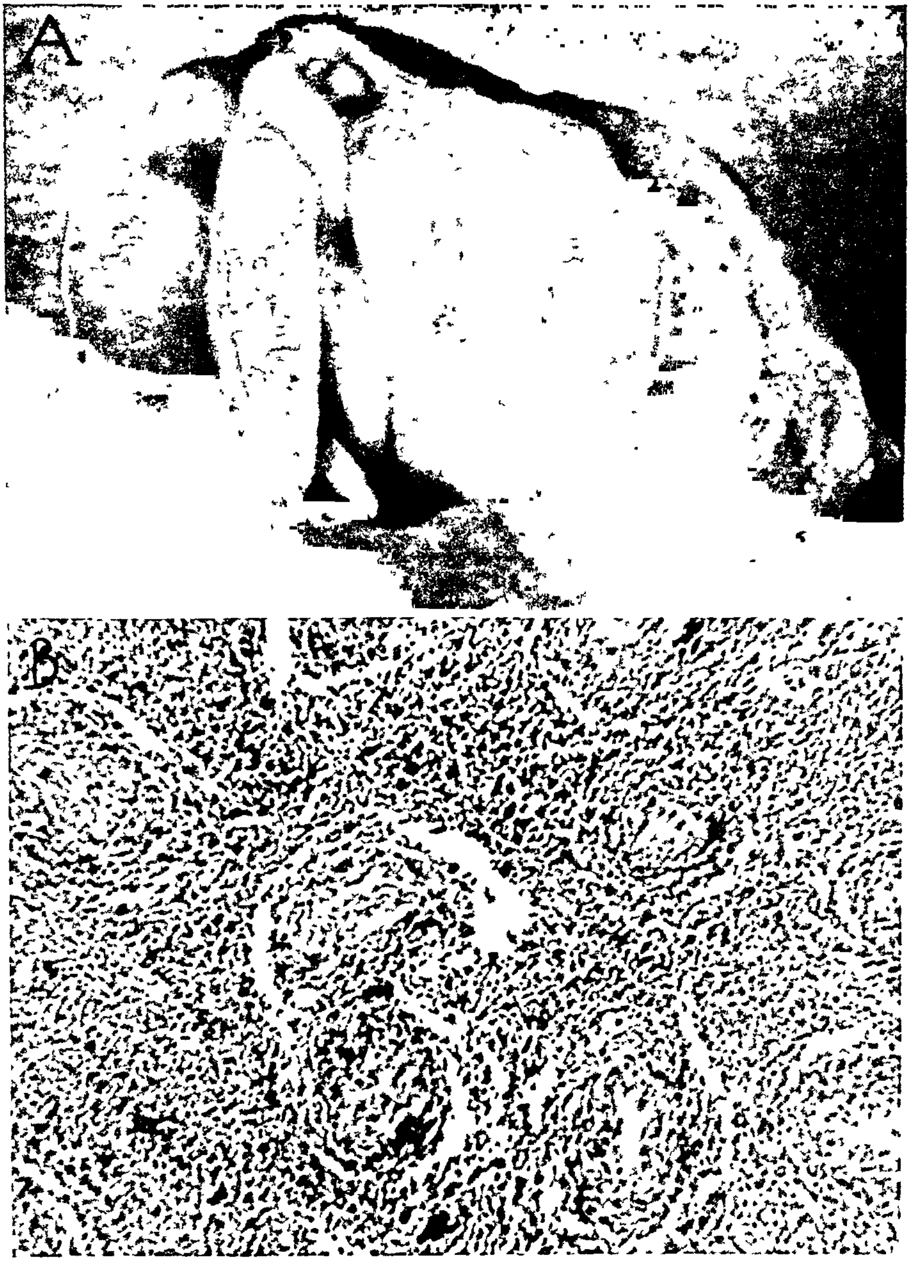

FIG. 1. Case 1 (GU Path No 7945). *A*, gross specimen. Testis diffusely involved by plasmacytoma. *B*, low power showing seminiferous tubules surrounded by invasive plasma cells.

died eight days after admission and at autopsy, a bilateral involvement of the testis by plasmacyt foun ry site was in the fifth thoracic vertebra. Recent iblished their necropsy findings in 38 cases of multiple myeloma In one of their cases a metastatic spread to the testis was found Their table on the incidence of extramedullary lesions compiled from a review of the 'world's literature' (182 cases, from 1892 to 1950), shows that the testis was involved five times They do not indicate, however, whether these were autopsy or operative findings

PATHOLOGY OF PLASMACYTOMA

Plasmacytoma tends to develop in bone marrow, particularly where red marrow is ordinarily found The bones most frequently involved, according to Anderson,[9] are the vertebrae, ribs, skull and ends of long bones Extramedullary origins are rare Males are affected in 70 per cent of the cases, and in 75 per cent the age incidence, in both sexes, is between 40 and 70 years The disease accounts for 3 to 25 per cent of all primary malignant tumors of bone[10] [11] and for 0 03 per cent[6] of malignancies of all types

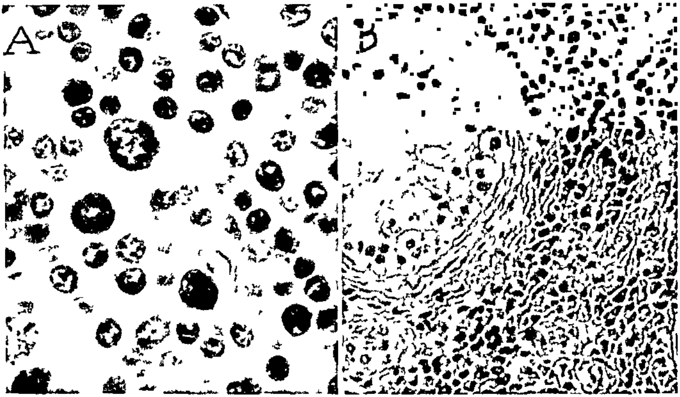

Fig 2 Case 2 (Path No 10661) *A*, plasmacytoma, biopsy Note characteristic "cog wheel" nuclei *B*, high power showing plasma cells filling stroma Note atrophic tubule

The component cells of plasmacytoma resemble plasma cells and occur in dense masses devoid of any intercellular substance The cells are small, round, or polygonal, and are deeply basophilic They usually possess eccentric nuclei whose chromatin tends to be clumped peripherally or show a coarse radial arrangement A paranuclear clear zone was often present Occasionally cells have two or more nuclei Mitoses are rare

The tumor nodules are usually soft, red, and vascular They are multiple in 90 per cent of cases but on occasion, only a single focus can be demonstrated The multi-focal origin of the disease is suggested by the observation by Willis[11] that the nodules, though numerous, may be of the same size so that not one is

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[8] Hayes, D W, Bennett, W A and Heck, F J Extramedullary lesions in multiple myeloma Arch Path, **53.** 262, 1952

[9] Ander, W A D St Louis C V Mosby Co, 1948

[10] Batts, M Multiple myeloma Review of 40 cases Arch Surg, **39.** 807, 1939

[11] Willis, R A Pathology of Tumors St Louis C V Mosby Co, p 786, 1948

specifiable as the primary focus. Expansion of a myeloma mass is usually accompanied by local absorption of bone and as a result a characteristic radiographic pattern is produced. The cell mass may protrude through the cortex of the bone and a spontaneous fracture may then occur.

Plasma cell tumors, apparently primary in, and restricted to the mucous membrane and submucous tissues of the alimentary tract and respiratory passages of the head and neck have also been reported by Clairborn and Ferris,[13] Kane et al.[14] They are very rare, affect mostly the nasal cavity and naso-pharynx particularly the tonsil.[15] They are relatively benign and the bones in such cases are usually free of tumor.

THE COURSE OF PLASMACYTOMA

With marked increase in the number of cells in a plasmacytoma, invasion of the bloodstream, i.e. plasma-cellemia, is apt to occur and metastases develop. On less frequent occasions the blood may become a culture medium for the plasma cells producing the picture of "plasma cell leukemia". The disease in either manifestation, is invariably fatal.

a) *Metastasis.* Intermittent introduction of myeloma cells into the bloodstream leads to the development of metastases. According to Willis,[11] tumors or diffuse infiltrations distant to the primary site occur in ⅓ to ¼ of the cases of plasmacytoma. Churg and Gordon,[16] however, found extramedullary involvement in 73 per cent of their cases. Hays et al.[8] report a 71 per cent incidence. They are of the opinion that the extramedullary masses which occur in organs rich in reticulo-endothelial tissue are of autochthonous development rather than metastatic. They are inclined to this view because the myeloma cell seems to arise from a reticulo-endothelial cell. The organs most frequently involved are the liver, spleen, lymph glands and kidney.[8, 16] Batts[10] states that in one-half of the autopsied cases, the liver, spleen and kidney contained nodules of multiple myeloma. Less frequently other organs and tissues such as the lungs, heart, skin, adrenal, thyroid, testes, ovaries, stomach, pancreas, uterus, dura mater,[17] and prostate may be involved.

b) "*Plasma-cell leukemia.*" The relationship between plasmacytoma and myeloid leukemia may be analogous to that between lymphosarcomatosis and lymphoid leukemia.[18, 19, 20] Cases of plasma-cell leukemia with active infiltration of the bone marrow but without destruction of bone have been reported by Lawrence and Fortner.[21]

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[12] Leger, H.: Myeloma, histobiologic study. Presse méd., **56:** 236–237, 1948.

[13] Clairborn, L. N. and Ferris, H. W.: Plasma cell tumors of the nasal and nasopharyngeal mucosa. Arch. Surg., **23:** 477, 1931.

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[15] Jackson, H. Jr., Parker, F. Jr. and Bethea, J. M.: Studies of disease of the lymphoid and myeloid tissues. Plasmacytoma and their relation to multiple myelomata. Am. J. M. Sc., **181:** 169, 1931.

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[17] Armstrong, E., Faulds, J. S. and Stewart, M. J.: Two cases of multiple myeloma (plasmacytoma) with secondary deposits in dura mater. J. Path. & Bact., **58:** 243, 1946.

[18] Klemperer, P.: Uber das Lymphoblastiche und das Plasmacellulare Myelom. Beit. z. path. Anat. u. z. allg. Path., **67:** 492, 1920.

The products of disintegrating plasma cells in a patient with plasmacytoma probably account for the following unique findings:

a) Bence-Jones proteinemia (hyperglobulinemia). Bence-Jones proteinemia occurs in about 70–80 per cent of cases of multiple myeloma and is usually associated with hyperglobulinemia (especially B), and inconstantly with proteinuria.[22] Evidence points to the myelomatous cells as the source of the protein. A serum protein level of more than 10 per cent is unusual in diseases other than plasmacytoma.[4] A hyperglobulinemia as high as 15.5 per cent has been recorded in this disease.[23] The combination of hypercalcemia with a normal or high serum protein level helps to differentiate this disease from hyperparathyroidism.[4, 24] Chester,[25] however, found normal serum and calcium in some of his patients with plasmacytoma.

b) Formol-gel reaction: The sera of most patients with kala-azar rapidly form a solid opaque white gel upon addition of 1–2 drops of formalin.[26] The test depends on the presence within the serum of increased amounts of globulin. In the presence of only moderate hyperglobinemia the test may be negative. The formol gel reaction was first proposed by S. Hetenyi[27] but he gave no data. Later Bing,[28] Wise and Gutman[26] recommended this test as a convenient preliminary one for detecting hyperglobinemia of diverse origin including plasmacytoma. A positive reaction adds confirmatory evidence for diagnosis of plasmacytoma but a negative one does not rule out this disease.

The hyperproteinemia in plasmacytoma may be so great as to cause autohemagglutination, a phenomenon reported by Reimann.[29] Rouleaux formation of red blood cells was also present and may have been the result of increased fibrinogen.

c) Bence-Jones proteinuria: The Bence-Jones proteinuria is demonstrable in about two-thirds of cases of plasmacytoma. The globulin-like substance *coagulates* at 50–60C (sometimes as low as 43–46C) and on heating goes into *solution* at about the *boiling point* (90–100C).[6] The precipitate *reappears on cooling* to 60C. If the precipitate does not disappear on boiling then albumen may be present. The latter may be eliminated by adding a few drops of 5 per

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[19] Churg, J. and Gordon, A. J.: Multiple myeloma with unusual visceral involvement. Arch. Path., **34:** 546, 1942.

[20] Stevenson, H.: Multiple myelomatosis: A clinico-pathological review with a report of a cas st. Grad. M. J., **24:** 269–282, 1948.

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hyperproteinaemia (late diagnosis of myeloma—the formol-gel teinuria and renal lesion). Acta. Med. Scand., **88:** 478, 1936.

erproteinemia as cause of autohemagglutination observed in a case of myeloma. J. A. M. A., **99:** 1411, 1932.

cent acetic acid, boiling and filtering the coagulated albumin. The test for the Bence-Jones globulin may then be repeated. It is important to note that the substance is not constantly excreted so that a negative test does not rule out plasmacytoma. Sandkühler[30] reports a reliable yet simple ring test for Bence-Jones protein.

d) Renal insufficiency: Renal disease is a common complication of multiple myeloma.[23] The distal convoluted tubules are frequently obstructed by dense acidophilic fragmented casts of Bence-Jones protein. The casts are at times lamellated. Many of the tubules show necrosis and in some desquamated epithelial cells fuse and form a syncytium about the casts. This is a distinguishing feature of myeloma nephrosis.[23] Rarely, the convoluted tubules contain needle-like crystals which vary considerably being either short or long, hexagonal or rhomboid; single or in packets.[31] They are not birefringent. The glomeruli usually show no specific changes. The degree of renal insufficiency usually varies with the extent of tubular obstruction and dilatation, tubular atrophy and parenchymal nephrosclerosis.

SYMPTOMS OF PLASMACYTOMA

The outstanding symptoms of plasmacytoma are pain and weakness.[4] The pain may not develop until injury to the diseased bone has occurred. One should consider the possibility of plasmacytoma in patients with unexplained pains in various parts of the body particularly backache when coupled with weakness. Geshickter and Copeland[6] found that in 40 per cent of their cases there was neurologic involvement:—radiculitis, paraplegia, etc. Patients with diffuse myeloma of the skeletal system may, however, be symptomless. The disease may resemble hyperparathyroidism because of the disturbed calcium balance.[32] In a report on 4 cases of plasmacytoma Foord[33] noted prolonged uncontrollable bleeding and an increased clotting time in spite of an increase in serum calcium and little change in blood platelets.

DIAGNOSIS OF PLASMACYTOMA

The diagnosis of plasmacytoma may be made on the basis of one or more of the following findings: a) A characteristic radiographic picture: Rosenthal,[34] however, points out that plasmacytoma may and often is present without radiographically demonstrable bone changes.

b) A positive sternal puncture as described by Rosenthal:[34] He reported 13 patients with multiple myeloma from the Mt. Sinai Hospital of New York. No characteristic findings were seen in the blood, a thrombocytopenia was present in five cases, myelocytes and myeloblasts were present in some, and the diagnosis in a number of cases was suggested by x-ray examination and laboratory findings (hyperproteinemia, formol gel reaction and Bence Jones's proteinuria) In *all the cases*, however, the diagnosis of plasmacytoma was established by simple *sternal puncture* Rosenthal states that the disease may be regarded as a generalized systemic one with involvement of the marrow of *all* bones

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[30] Sandkühler, S.: Simple test for Bence-Jones protein. Am. J. Clin. Path., **22**: 283-284, 1952.

[31] Sikl, H.: A case of diffuse plasmacytosis with deposition of protein crystals in the kidneys. J. Path. and Bact., **61**: 149-163, 1950.

[32] Enzer, N.: Multiple myeloma. Ann. Int. Med., **8**: 1062, 1935.

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[34] Rosenthal, N. and Vogel, P.: Value of sternal puncture in the diagnosis of multiple myeloma. J. Mt. Sinai Hospital, **4**: 1001, 1938.

c) Bence Jones proteinuria This is an inconstant finding and the test should be repeated several times
d) Bence Jones hyperglobulinemia
e) Formol gel
f) Renal findings

CASE REPORTS

Case 1 A K (No 873366), male, aged 54, was admitted to the Presbyterian Hospital with a 4 month history of transitory joint pains, usually involving the lower part of the right leg The left ankle, knees and elbows were also affected but to a lesser degree The patient had been treated with colchicine, neocinchophen and purine free diets without success He lost 15 pounds in 4 months Examination disclosed an extremely tender swollen right ankle with swelling extending halfway up the tibial shaft There was no redness, nor was there any limitation of motion Walking was possible with the aid of a cane The radiographs of the right tibia revealed numerous punched out areas characteristic of plasmacytoma The blood uric acid was 4 4 per cent

Two pieces of soft greyish tissue were removed from the right foot and sectioned They showed connective tissue and fat diffusely infiltrated by densely packed round to polygonal cells with large hyperchromatic nuclei Mitotic figures were rare The stroma was scanty and moderately vascular The morphology of the cells was compatible with a diagnosis of plasmacytoma This opinion was tenable in spite of the absence of bone in the specimen because the disease can infiltrate from bone into surrounding soft tissues An enlargement of the right testicle was noted and he was then transferred to the Squier Urological Clinic Excretory urography was negative The following were some of the laboratory findings Cholesterol 209 mg per cent, serum alkaline phosphatase 4 3 b u , serum acid phosphatase 1 3 b u , serum protein 6 0, albumin 4 4, globulin 2 5 The urine was essentially negative and the Bence Jones reaction was negative

Under pentothal, gas, oxygen and ether anaesthesia, a right orchiectomy with high ligation of the cord was performed The following is a resume of the pathology report (No 7945) The specimen weighed 100 gm and consisted of testis, portion of the cord and epididymis Sections revealed a diffuse infiltration by a tumor composed of cells like those seen in the biopsy of the foot The plasma cells infiltrated between seminiferous tubules and compressed them The picture was characteristic of metastasis The epididymis was also invaded Diagnosis Plasmacytoma of testis and epididymis secondary to plasmacytoma of bone

Radiographs of the skull, pelvis, chest, legs, ankles showed lesions similar to those previously noted in the right tibia There was extensive destruction of the calcaneus The patient was given nitrogen mustard for the disseminated bone lesions. He died at his home 8 months following his first admission to the hospital (12 months after the onset of symptoms). Prior to his death he suffered from spontaneous fractures of his right arm and both legs.

Case 2. M. J. (No. 065976), a 62-year old physician, was admitted to the Squier Urological Clinic complaining of a painful swelling in the right epididymis of 3 months' duration and of marked fatigability. A sternal bone-marrow biopsy had been obtained by Dr. N. Rosenthal and it revealed as follows:—

BONE MARROW	PER CENT	NORMAL
Nucleated cells .	47,000	100,000
Megakaryocytes	22	44
Myeloblasts		0–3
Progranulocytes		0–4
Myelocytes		
Neutrophilic	7.6%	10–30
Eosinophilic	1.3%	0–4
Basophilic		0–1
Metamyelocytes	5.0%	3–10
Band cells	6.6%	10–30
Segmented		
Neutrophilic	4.3%	10–30
Eosinophilic	0.6%	0–4
Basophilic		0–0
Plasmacytes	67.0%	0–3
Lymphocytes	1.3%	1–15
Hematogenes		1–10
Reticulum cells		0–2
Rubriblasts ..		0–0
Proerythroblasts		0–1
Rubricytes (erythroblasts)	2 0%	2–15
Metarubricytes (normoblasts)	4 0%	7–30

Conclusion: "The bone marrow is typical of multiple myelomatosis" (plasmacytoma).

Other laboratory findings were:

Blood Count·	Hemoglobin	9 3 gm. (59%)
	Red cells	3,440,000
	White cells	5,500
	Platelets	180,000
	Polys Band	2.5%
	Polys Seg.	59.0%
	Polys Eos.	2.0%
	Lymphocytes	26.0%
	Monocytes	10.5%
	Reticulocytes	0.2%
	Hematocrit	32%

Liver function tests Cephalin flocculation, negative, formol gel, positive, icterus index, less than 3, thymol turbidity, 3 units, Coombs test, negative "There is no evidence of liver dysfunction but a marked increase in the globulin as indicated by the prompt formol gel reaction" Albumin 1 9, globulin 7 4, total protein 9 3, *sedimentation rate 136 mm in 1 hour (normal up to 15)*

Examination revealed a well developed male, not acutely ill The right epididymis and testis were enlarged and markedly tender The prostate was normal in size and consistency The right testis was removed under general anaesthesia A summary of the pathological report (No 10661) is as follows The specimen consists of testis, epididymis and 13 cm of the cord The sections show a neoplasm composed of cells that resemble plasma cells The latter have surrounded and compressed seminiferous tubules The epididymis is not involved Diagnosis Plasmacytoma involving right testis

The patient made an uneventful recovery and resumed his practice of medicine However, the pronounced fatigue persisted and within a month the severe backache returned Radiographs revealed destruction of the twelfth rib and first lumbar vertebra He grew steadily weaker and died 1½ months after operation (4½ months after onset of symptoms)

Case 3 P G (No 612901), male, age 63, was admitted to the Presbyterian Hospital with the complaint of weakness of 1 year's duration He also suffered from dyspnea, epigastric distress and crampy pains in the upper abdomen Frequency and nocturia with slight dribbling developed 2 months prior to admission A small tender lump had been present in the skin of the anterior chest wall for 3 weeks Fever and chills were also noted

Examination revealed a pale, white male, not acutely ill Two nodules were now present in the area just described The liver margin was palpable 4 fingers below the costal margin The rest of the examination was negative Laboratory findings were Hemoglobin 48 per cent, red blood cells 2,680,000, white blood cells 5,900, Differential normal, platelets 201,000 Urine specific gravity 1018, albumin 2-3 plus Urine was positive for Bence Jones protein ESR 80 mm/hr The stool was negative for guaiac The Kline test was negative The serum protein was 8 2 per cent, albumin 6 2 per cent, globulin 2 per cent, englobulin 0, inorganic phosphorus 5 4 mg per cent, phosphatase 7 0 b u , calcium 11 0 mg per cent, nonprotein nitrogen 54 mg per cent, bilirubin 0, cholesterol 163 mg per cent, acid phosphatase 1 3 b u , magnesium 3 1 mg per cent, potassium 4 8 mil per liter Sodium 138 2 mil per liter Serum CO 57 7 vol per cent Chloride as sodium chloride 103 2 mil per liter Uric acid 9 9 mg per cent Skeletal x rays showed numerous round irregular areas of diminished density in the skull, the upper humeral shafts, the spine and the head of the left femur Biopsy of a skin nodule (S X74912) was reported as "probably atypical lymphosarcoma" In spite of radiotherapy and supportive measures, the patient continued to have pain, and grew steadily weaker He died 4 months after admission and 16 months following onset of his symptoms

Autopsy (No 13476) revealed a plasmacytoma involving vertebrae, ribs, sternum and skull The kidneys showed lesions that are occasionally seen in plasmacytoma They were enlarged The right weighed 160 gm and the left

180 gm. The tubules, particularly the convoluted tubules were frequently filled with dense acidophilic casts. Many tubules showed necrosis, and in some the epithelial cells had been desquamated and become adherent to the casts. The left testis was involved by a tumor composed of plasma cells. The cells infiltrated through the stroma and separated the tubules widely. Anatomical diagnosis: Multiple myeloma (plasma cell type)—vertebrae, ribs, sternum and skull; secondary myeloma in retroperitoneal lymph nodes, retroperitoneal tissues, skin and testes.

Case 4. S. G. (No. 651929), male, aged 50, was admitted to the Presbyterian Hospital with pain in the scapular region of 5 months' duration. One month after onset of his illness a severe cough and bandlike pain developed across the lower chest. Radiographs revealed erosion of T7 and 8 vertebrae. Examination showed an acutely ill, profoundly weak adult male lying still because any motion caused severe chest and back pain. The liver edge extended 2 cm. below the costal margin. There were no significant palpable masses.

Laboratory findings were as follows: Hemoglobin 6.8 gm.; 47 per cent; red blood cells 2,200,000; white blood cells 4,000 (reticulocytes 0.57 per cent); neutrophiles 79 per cent (0-30-49); eosinophiles 3 per cent; L. 18 per cent; mean cell diameter 9.0 micra. EXR 8/13: 150 mm. Urine: specific gravity 1.012; Bence-Jones 4+; albumin also present; 4 red blood cells per high power field. Stool guaiac negative. Gastro-intestinal series 30 per cent 6-hour residue. X-rays for 24 hours; stomach moderately dilated; position high; gastric walls flexible. No evidence of ulcer. Deep erosion left side to T11; deep notched outer margin of L1. Defect narrow, right border of T12. Serum inorganic phosphorus 6.7 mg. per cent; phosphatase 2.6 b.u. per cent; calcium on one occasion 14.0 mg. per cent; nonprotein nitrogen 60 mg. per cent; bilirubin 0. Protein 13.6 per cent; albumin 3.7 per cent; globulin 9.9 per cent; euglob. 7.2 per cent.

Additional radiographs revealed fractures of T7, T8, L2 and L4 vertebrae and erosion of L5. All the vertebrae showed diffuse demineralization. Five days after admission the temperature rose to 103.4F, the pulse to 150 and respirations to 60. The patient became more dyspneic and cyanotic and died on the ninth hospital day.

The following were the autopsy diagnoses:—Autopsy No. 13696. Multiple myeloma (diffuse meylomatosis)—plasma cell type, secondary myeloma in liver, spleen, kidneys and testis. Pathological fractures of ribs (R1, R2, L3, L6, and L7) and vertebrae (T8 and L2); Bence-Jones proteinemia (clinical); Bence-Jones proteinuria (clinical); nephrosis due to Bence-Jones protein.

SUMMARY AND CONCLUSIONS

Four cases of plasmacytoma metastasing to the testis have been presented. In two, the testicular involvement was found at operation and was the only evidence at that time, of metastatic spread from the primary focus in the bone marrow. In the other two cases autopsy revealed that the lesion in the test's was part of a diffuse metastatic process.

The vertebrae, ribs, skull and end of long bones are the most frequent primary sites of plasmacytoma. Multiple foci are seen in 90 per cent of cases, males are affected in 70 per cent and in 75 per cent the age incidence, in both sexes, is between 40 and 70 years

The outstanding symptoms are persistent backache, sometimes radicular in character, or vague generalized pains, accompanied by progressive weakness The testicular involvement was usually symptomless, the lesion being discovered either accidentally in routine examination or at autopsy

Inundation of the blood stream with neoplastic plasma cells may result in plasma cell leukemia

The products of disintegrating plasma cells probably account for many of the laboratory findings in plasmacytoma The Bence Jones hyperglobulinemia occurs in 70–80 per cent of cases Increased amounts of globulin with the sera tend to give a positive formol gel reaction The Bence Jones proteinuria, an inconstant finding, depends on the spilling over from the serum through the kidneys of the excess globulin Rosenthal regards plasmacytoma as a generalized systemic disease involving the marrow of *all* bones and has found sternal puncture to be the most reliable single test

Renal insufficiency is a common complication of plasmacytoma The distal convoluted tubules may become obstructed by dense acidophilic fragmented casts of Bence Jones protein The casts may be lamellated Desquamated epithelial cells fuse and form a syncytium about the casts Needle like crystals may rarely occur

The secondary involvement of the testes may be of microscopic size and discoverable only when sections are prepared Extensive infiltration causes enlargement of the organ A dense, diffuse infiltration with cells that resemble plasma cells is seen The stroma between seminiferous tubules is flooded and the tubules are compressed

The disease is invariably fatal

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INTERSTITIAL CELL TUMOR OF THE TESTIS: A CASE REPORT AND REVIEW OF THE LITERATURE

P. L. BATES, A. J. WILETS AND H. J. COKELY

From the Department of Urology, United States Naval Hospital, St. Albans, N. Y.

A review of the world literature confirms the impression that interstitial cell tumors of the testis are rare. To date a total of 40 cases have been reported, 27 being present in adults and 13 in children. There have been several reviews of the literature[1, 2, 3] the most recent being by Melicow et al.[4] It is our purpose to report the forty-first case of interstitial cell tumor and bring the current literature up to date.

CASE REPORT

F. L., a 29 year old unmarried white man, was admitted on June 22, 1952. One week prior to admission, during the course of a routine physical examination, a hard mass was found in the right testicle. He had no subjective symptoms and his past history was non-contributory. His physical and psychosexual maturation had apparently been normal and there had been no current change in physical characteristics or libido. Physical examination revealed a well nourished, well developed white male who appeared to be his stated age. His height was 5 feet, 7 inches; weight 159 pounds. Blood pressure 140/90. He had a normal male distribution of hair and there was no evidence of abnormal fat distribution. The left testis was of normal size but the upper two-thirds was firm, nodular and well demarcated from the lower one-third. The right testis was normal to palpation. The prostate was of normal size and consistency. Routine blood and urine studies were found to be within normal limits. Preoperative urine studies of pituitary and chorionic gonadotrophins were performed. The follicle stimulating hormone assay was positive for 52 mouse units and negative for 104 mouse units (normal range for both men and women in the premenopausal ages is 6 to 50 mouse units).[5] On the day following admission a right orchiectomy was performed with ligation of the spermatic cord at the internal inguinal ring. Urinary neutral 17-ketosteroids examined on the second postoperative day were 5.1 mg./24 hours (normal adult range is 6–22 mg./24 hours).[5] Semen analysis on July 10 (2 weeks postoperatively) revealed an oligospermia of 13,800,000 active spermatozoa/total specimen. The patient had an uneventful postoperative course and was discharged from the hospital on July 10, 1952.

The testicle and spermatic cord had an aggregate weight of 41 gm. The testicle measured 4.5 by 3.5 by 2.5 cm. and there was an attached spermatic cord of 15 cm. The tunica albuginea was shiny and gray-white. The middle and su-

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The views expressed are those of the authors and are not to be construed to represent those of the United States Navy or of the Naval Service at large.

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[1] Stewart, C. A.: Am. J. Cancer, **26:** 144, 1936.

[2] Hunt, V. C. and Budd, J. W.: J. Urol., **42:** 1242, 1939.

[3] Huffman, L. F.: J. Urol., **45:** 692, 1941.

[4] Melicow, M. M., Robinson, J. N., Ivers, W. and Rainsford, L. K.: J. Urol., **62:** 672, 1949.

[5] Soffer, L. F.: Diseases Of The Adrenals. Philadelphia: Lea and Febiger, 1948, 2nd ed.

perior portions of the testicle were indurated but did not bulge from the surface On cut section in the superior pole there was an encapsulated, tan-gray nodule measuring 3 by 2 by 1 5 cm which could be easily shelled away from adjacent testicular parenchyma (fig 1) The tumor was firm and lobulated The remainder of the testis appeared normal except for some compression The spermatic cord demonstrated no gross abnormality

Microscopic The encapsulated tumor was composed of islands and sheets of tumor cells separated by broad connective tissue bands (fig 2) The cells were uniform and of moderate size with pale acidophilic cytoplasm The nuclei were round or oval, of moderate size and with relatively large eccentrically placed nucleoli (fig 3, A) These cells resembled hepatic or adrenal cells Many were vacuolated and a few were foamy A rare mitotic figure was encountered Scattered degenerating tumor cells had intensely red staining cytoplasm and pyknotic nuclei Atrophic seminiferous tubules were noted in some areas adjacent to the tumor but others appeared normal with active spermatogenesis (fig 3, *B*) Small nests of Leydig cells were present Lipofuchsin and sudanophilic material were revealed in small quantities by fat stains on frozen sections Safranin red stains failed to disclose any crystalloids The adjacent epididymis was not remarkable Sections of the spermatic cord examined were found to be normal

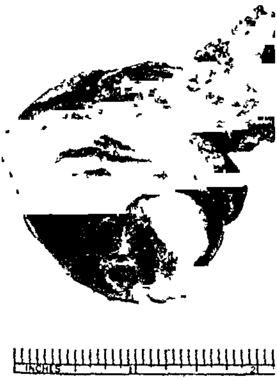

FIG 1

DISCUSSION

The interstitial or Leydig cells of the testis are cells of connective tissue origin, lying singly or in groups in the spaces between the seminiferous tubules

Early in human fetal development (10–12 mm embryo) the interstitial cells are adjacent to and even confluent with the cells which later become incorporated in the adrenal cortex At this level of maturation the adrenal cells are indistinguishable from the interstitial cells[6] At 16 mm a nidus of tissue at the

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[6] Personal communication Dr Roy E Crowder

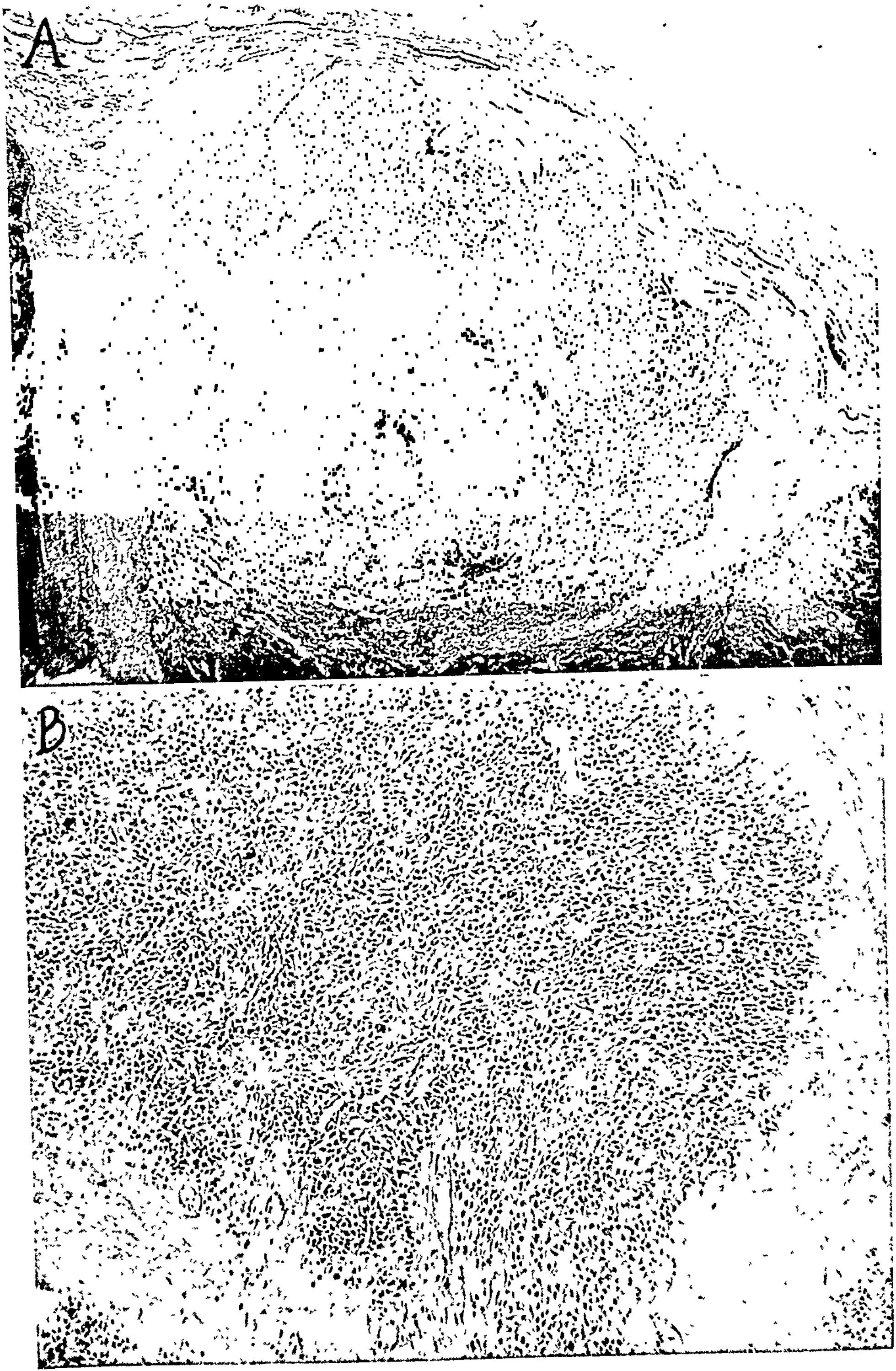

FIG. 2

mesonephric cap begins to proliferate rapidly and further growth with the formation of a capsule at 25 mm. separates the adrenal cortical cells from the interstitial cells.

The relatively numerous interstitial cells during fetal life decrease after birth to be replaced largely by fibrous tissue. As puberty approaches they increase in number again. During adult life there is a relative decrease in the interstitial cells, but not so marked as was formerly believed. With senility a relative increase in the number of interstitial cells is apparent while seminiferous tubules atrophy.

Normal interstitial cells are 14–21 microns in length, spheroidal or oval, and possess a small round eccentric nucleus. In the fresh state the acidophilic cytoplasm of the interstitial cells is filled with highly refractile granules of neutral fat and lipids. Fat droplets may or may not be present in interstitial cell tumors. Intracytoplasmic lipofuchsin granules are commonly present in the normal and pathological state. Reinke's crystalloids are rod-shaped inclusions 1 by 1 by 10 microns in diameter characteristically seen in the normal interstitial cells while rarely observed in interstitial cell tumors.[7] The nuclei of interstitial cells contain one or more prominent nucleoli. Mitoses are usually absent but rarely may be abundant.

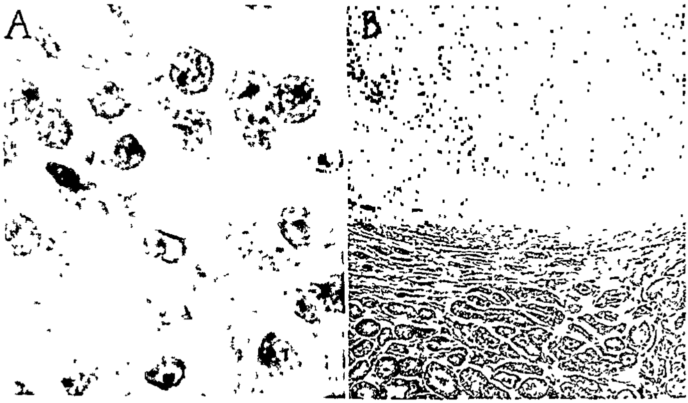

Fig. 3

Simple hyperplasia of the interstitial cells is not uncommon and is usually differentiated easily from interstitial cell tumors by the absence of a capsule or lobulations and the presence of seminiferous tubules interspersed through the hyperplastic areas. Hyperplasia has been observed in chronic cachectic illnesses, chronic alcoholism, severe acute illnesses particularly pneumonia, cryptorchidism, and testicular atrophy due to local disease.

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[7] Friedman, N. B and Ash, J E: Atlas of Genito-Urinary Pathology. Army Institute of Pathology, Washington, D. C., Government Printing Office, 1946.

The interstitial cell tumor is nearly always nodular and may or may not b encapsulated. The cut surface is light tan to yellow to brown. The size of th tumor varies. The average size of the reported Leydig cell tumors is considerabl less than the average size of the more common testicular neoplasms.

The vast majority of reported interstitial cell tumors have been benign. Th degree of malignancy in any given Leydig cell tumor must be judged cautiousl almost in retrospect. Only five patients with a malignant tumor have been reported. In one of these patients metastases appeared four years after the origina operation and in another 10 years following orchiectomy. Gharpure[8] has offere four histological characteristics of malignancy: 1) marked pleomorphism of th cells, 2) giant atypical mitoses, 3) lack of brownish pigment in the cytoplasm and 4) tumor cell emboli in lymphatic vessels.

Table 1. *Interstitial cell tumors: Adrenal rest tumors*

Color	Varied, usually light, occasionally dark brown	Dark brown
Bilaterality	Rare	Bilateral
Pattern of cell growth	In large sheets, masses or cords; never in small nests	Small nests and individua elements
Vascular pattern	Small networks of capillaries between cell groups	Innumerable vascular channels, frequently sinusoidal capillaries
Associated hyperplasia of adrenal cortex	Never described	Present

Histologically these neoplasms closely resemble adrenal cell rests or androblastomas. Due to the histological and embryological similarity between primordial adrenal cortex cells and interstitial cells of the testis, it is not surprising that difficulties in differentiation would arise. The incidence of adrenal cell rests within the substance of the testis is extremely rare as judged by the dearth o reported cases.

Cohen[9] reports a case of bilateral testicular tumors of adrenal cell rests in an adult. The patient had a precocious sexual development at 6 years of age. Medical advice was sought at this time but no definitive treatment was given. He entered the Army and while in the service died after a 12 hour illness precipitated by pneumonia and adrenal shock. At autopsy, Cohen states, adrenal rests were found replacing practically all of the interstitial cells in each testis. There was extreme adrenal cortical hyperplasia bilaterally. The Ponceau stain which is reported to be selective for adrenal cortical cells was not taken up by either the adrenal or the testicular growths in this case. Cohen mentions the similarities between the interstitial cell tumors and androblastomas. On the basis of his findings, he offers the distinctive features shown in table 1.

In our patient the foregoing mentioned characteristics of adrenal rest tumors were not present The absence of crystalloids in our case does not strongly militate against the diagnosis of interstitial cell tumor for while present in normal interstitial cells they have been rarely encountered in interstitial cell tumors

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[8] Gharpure, V. V.: J. Path. and Bact., **57**: 113, 1950.

[9] Cohen, H.: Am. J. Path., **22**: 157, 1946.

The preoperative diagnosis of interstitial cell tumor of the testis can be strongly suspected in a child showing precocious sexual development and presenting a testicular mass In adults a preoperative diagnosis is unlikely to be made but can be suspected at the operating table when an encapsulated, parenchymal, light tan mass is encountered

The incidence of interstitial cell tumors as reported by Friedman and Moore[10] is 1 per cent in their series of 922 testicular tumors This ratio seems high to some observers as there are only 40 cases in the world literature excluding their own, who to our knowledge have not been reported individually

Interstitial cell tumors occur at all ages The youngest reported patient was 1½ years old, the oldest was 82 years The overall age incidence is 30 1 years The average of 28 adults having the tumor is 39 9 years Of the 13 cases in children, the age incidence is 7 8 years Hormonal changes (virilism) were present in all children Endocrine changes were the exception in adults Four adults were reported with bilateral gynecomastia, six gave a history of decreased libido, two of impotence

Why should an interstitial cell tumor which invariably produces virilism in the prepubital patient occasionally produce in adults feminizing effects? Are the five reported interstitial cell tumors which were apparently responsible for the appearance of bilateral gynecomastia actually Sertoli cell neoplasms? A benign feminizing testicular tumor arising possibly from poorly differentiated Sertoli cells is reported by Lewis and Stockard[11] This 68 year old patient had normal excretion of 17-ketosteroids and gonadotropins Urine pregnandiol determinations were elevated An encapsulated light yellow testicular tumor was removed measuring 6 5 cm in diameter Nine months after orchiectomy the gynecomastia had disappeared Pregnandiol excretion in the urine was normal The cytology of the tumor resembled granulosa cells of the ovary but were not unlike interstitial cells either The diagnosis of interstitial cell tumor was rejected on a pathological basis by the authors They state that interstitial cell tumors are not well encapsulated and are a brick or orange-yellow color In our review of 14 interstitial cell tumors[8, 12-22] these criteria are not confirmed (table 2) Nevertheless the leuteinizing activity of the tumor was evident in their

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[10] Friedman, N B and Moore, R A Military Surg , 99: 573, 1946
[11] Lewis, L G and Stockard, C C J Urol , 64: 518, 1950
[12] Price, I I Brit J Surg , 36: 81, 1948
[13] Scully, R E and Parham, A R Arch Path , 46: 229, 1948
[14] Reiners, C R and Horn, R C Jr Am J Clin Path , 19: 1039, 1949
[15] Fraser, K B Austral & New Zealand J Surg , 19: 48, 1949
[16] James, D C and Shupe, R D J Urol , 63: 718, 1950
[17] Tedeschi, C G and Burke, F E Cancer, 4: 312, 1951
[18] Grabstald, H , Haines, J S and Morrow, A G J Urol , 66: 708, 1951
[19] Garvey, F K and Daniel, T B J Urol , 66: 713, 1951
[20] Flynn, P T and Severance, A O Cancer, 4: 817, 1951
[21] Bohls, S W and Flynn, P T Abstracted Case Report Tex State J Med , 47: 574, 1951
[22] Newns, G H Brit J Surg , 39: 379, 1952

TABLE 2. *Interstitial cell tumors of testis reviewed from the literature*

CASE	DATE PUBLISHED	AGE OF ONSET OF SYMPTOMS	AGE AT OPERATION	MALE SEXUAL CHANGES	EXCESSIVE GROWTH FOR AGE	GYNECOMASTIA	HORMONAL DETERMINATIONS		POST-OP. SEXUAL CHANGES	BENIGN OR MALIGNANT	COLOR & DIAMETER OF TUMOR	ENCAPSULATION	CRYSTALLOIDS	PATHOLOGY QUEST.	CLINICAL FOLLOW-UP
							Pre-op.	Post-op.							
Price	1948	? "hernia"	53	none	—	no		none	none	presumed benign	grayish brown 1.5 cm	yes	not stated	no	1 year
Scully & Parham	1918	53	55	none	—	no		none	none	benign	grayish 8 cm	yes	not stated	no	10 years, death, hear disease, au topsy
Reiners & Horn	1949	33	33	increased libido 5 mo., dec. 1 mo.	—	no		17 K-S, N. gonadotrophins 168 mμ 2 mo., N 18 mo.	libido N	presumed benign	yellow gray 2.5 cm	partial	not stated	no	1½ years
Reiners & Horn	1949	51	51	none	—	no		17 K-S, N gonado., N. estrogen, N.	none	presumed benign	tan 2.0 cm	yes	not stated	no	7½ mo.
Fraser	1949	2	4	yes, hair, voice & penis	looked 10 yrs. bone age 6½ yrs.	no	A-Z neg.		hair disappeared penis smaller	presumed benign	red brown 1.5 cm	no	not present	no	6 mo.
Gharpure	1950	45	45	none	—	no		none	*none*	malignant	yellow brown 8.5 cm	partial	not present	yes	death 9 mo metastases skull, lungs
James & Shupe	1950	9	14	hair & voice 9 yrs. libido 11 yrs.	looked 25 yrs.	no		17 K-S, 9.8 at 3 mo.	none	presumed benign	light brown 6 cm	no	not stated	yes ?adrenal rests	13 mo.
Tedeschi & Burke	1951	? "hernia"	57	not stated	—	not stated		none	—	malignant	grayish pink 4.5	paratesticular	not present	yes ?adrenal rests	death 45 day ascitic fld tumor cells no autopsy
Grabstald, Haines & Morrow	1951	28	32	decreased libido 2 yrs.	—	bilateral	Friedman negative		? change libido regressed gyneco.	benign	brown 1.0 cm	yes	present	no	death, 1 yr cor. throm bosis autopsy
Garvey & Daniel	1951	14	19 bilateral	decreased libido	all extremities shortened	no	Friedman negative		no	presumed benign.	dark brown 7 cm & 6 cm	partial	not present	no	1 yr.

ynn & rverance	1951	24	26 bilateral	decreased libido	—	no		none	no	presumed benign	dark brown 6 cm & 3 cm	partial	not present	no	3 yrs
ihls & ynn	abstracted 1951	?	22 & 26 bilateral	?	?	?		?	?	presumed benign	grayish brown 6 cm greenish brown 3 cm	?	not stated	yes	1 yr "living & well"
wns	1952	1½	2	yes, hair, voice & penis	yes, bone age 8 yrs	no	17 K-S 13 5	17 K-S 0 98, 8 days p o.	yes, all features	presumed benign	yellow, & red dots 3 2 cm	yes	not present	no	1½ yrs.
lets & tes	1952	29	29	none	—	no		17 K S 5 1 Gonado trophins (FSH) 52 mμ	no	presumed benign	grayish tan 3 cm	yes	not present	no	1 mo.

case. This endocrine effect would be more logically explained, as they state, by assuming that interstitial cells were not responsible. Lewis and Stockard[11] review 4 cases (Huffman, Hunt and Budd, Monaschkim, and Teilum) and describe the similarities to their patient.

Hormonal changes in adults which are sufficient to produce gynecomastia and impotence resemble to some extent the effects seen in the extremely rare cases of adrenal cortical tumors resulting in the feminizing syndrome.[23]

Does the interstitial cell tumor in adults produce an excess of circulating androgenic substances? No case has been reported in which the patient manifested any signs of increased virilism. Nor did we find an elevated 17-ketosteroid excretion reported in any adult patient.

In our patient 17-ketosteroid and pituitary gonadotropin outputs in the urine were within normal range; however, both were borderline. It is regrettable that estrogen and androgen assays were not done on the tumor tissue in our patient prior to fixation in formalin. The oligospermia in our patient had no specific cause that we could determine and imposes an interesting but admittedly questionable relationship to the hormonal findings.

SUMMARY

The case of a patient with an interstitial cell tumor of the testis is presented. The literature on this subject is brought up to date.

The preoperative diagnosis can be strongly suspected in children. In adults the diagnosis is considered after inspecting the gross specimen.

The similarity in the embryological development of interstitial cells and adrenal-cortical cells is discussed.

The difficulties of differentiating interstitial cell tumors from adrenal rests is presented.

The feminizing effects occasionally seen in patients having interstitial cell tumors and other testicular tumors are discussed.

The authors wish to express their appreciation to Mr. R. Schroeder and Mr. M. Russen for their technical assistance in the pathological preparation and photography respectively.

[23] Mortensen, H. and Murphy, L.: J. Urol., 65: 709, 1951.

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ADRENALECTOMY FOR ADRENAL TUMORS

GEORGE F CAHILL

Operative removal of the involved adrenal when tumor is present is, up to now, the only method of cure A certain cure is obtained if the tumor is benign, provided all the tumor is removed, and a probable cure may be obtained if a malignant tumor is removed before it metastasizes

Certainly the method of removal will vary greatly depending upon whether the tumor is benign or malignant Also, it will depend upon the expansion of the tumor in its growth, whether upward into the hollow of the diaphragm or downward and anterior to the kidney, making an approach to be more feasible if made in the area of expansion Also, since some of these tumors often may be multiple, like pheochromocytoma, the approach should be in the fashion that all possible tumor areas may be explored Again there will necessarily be considerable variation in the preparation and handling of the surgical subject in the case of certain hormonal tumors that make considerable alteration of the metabolism of the patient, and increasing risk to the operative procedure The surgery of these tumors has seen great interest and improvement due to a number of recent advances

1) Increased knowledge of the functions and secretions of both the adrenal cortex and medulla

2) Identification and production of steroids of the cortex which when administered can replace the necessary hormones of the cortex and maintain life

3) Identification and production of the catechols of the medulla

4) Increased experience with the syndromes in adrenal functional changes and the diagnostic procedures by assay

5) Improved technical surgical procedures including those of anesthesia and control of infection

6) Widespread interest and investigation which continue to disclose the many as yet unknown factors concerning the influence of the adrenals on metabolism

When tumors occur in the adrenal they can be divided into the following classification

1) *Stromal tumors* These are similar to the stromal tumors in any other gland They occur rarely The following types have been reported fibroma, lipoma, neuroma, neurofibroma, myoma, osteoma, hemangioma, sarcoma, lymphangioma and melanoma

2) *Medullary cell tumors* These derived from ectodermal sympathetic system occur more frequently and are of the following types a) From the embryonic sympathetic nerve cell, a sympathicoblastoma, b) from the sympathetic ganglion cell, a ganglioneuroma or neurocytoma, and c) from the pheochromocyte, a hormonal cell, a pheochromocytoma

3) *Cortical cell tumors* These, originating from the mesodermal glandular cells of the cortex, are benign adenomas and carcinomas, and symptomatically may be nonhormonal or hormonal

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STROMAL TUMORS OF THE ADRENAL

These extremely rare tumors may be either benign or malignant. The benign tumors, such as fibromas or lipomas, are usually without symptoms unless they expand large enough to cause distress by their size alone. They, few as they are, more frequently have been discovered by accident on examination or at operation. Their removal requires no special operative preparation for anesthesia or for metabolic changes. They have been and may be safely removed through the flank or transperitoneally at the time of correction of other pathological change. The blood vessels are usually not large or fragile. They are well encapsulated, shell out easily and mostly may be separated from normal adrenal which may be retained. The normal adrenal often separates with difficulty due to friability and its bleeding, although slight, requires patience to control. The results have been mostly satisfactory.

When tumors of this group are malignant an entirely different situation is present. Mostly there is an entire absence of symptoms until metastasis or spread has occurred and then there occurs loss of strength, weight, anemia and abdominal distress depending upon the extension of the tumor. Studies may show evidence of invasion of the kidney which seems to be the most frequent route of extension and they may be mistaken for renal tumors. Operative removal may be through the flank, through the diaphragm, transthoracic or through the peritoneum, preferably by transverse incision. The transthoracic diaphragm exposure or the transverse transperitoneal route offers a wider exposure on attempt to remove the tumor and involved areas, because removal offers the better chance for correction. Most often removal has been impossible; the diagnosis has been established by biopsy, and the case treated later by high voltage x-ray. With the exception of certain lymphosarcomas most of these tumors have a relatively high degree of radio-resistance and the usual course has been extension and death.

TUMORS OF THE ADRENAL MEDULLA

Sympathicoblastoma. This is perhaps the more frequently seen tumor of the adrenal medulla, an extremely malignant growth, occurring most frequently in infancy and childhood and rates in seriousness with the renal embryomas of Wilms. They occur in either sex and in either gland and may also occur in other sympathetic ganglia. They occur less frequently as age progresses.

The original tumor is usually symptomless and its discovery is frequently accidental or found in only an enlarging abdomen. More often it is the metastases which attract attention to the condition. The historical description by Hutchinson and Pepper of the metastases to the skull, especially the orbit and, in the other, to the liver and thorax, still holds. In others with anemia and bone changes as shown by x-ray, the diagnosis is only established by biopsy of the secondaries.

Occasionally, the tumor has been recognized before metastases are demonstrable. If so, the tumor may resemble the flank or abdominal mass as with Wilms's tumors. These masses are without pain or tenderness. Handling of the mass is precarious to the patient and should be avoided completely. The diagnosis may be expedited by old fashioned transillumination to rule out an obstructed functionless hydronephrosis, and by secretory urograms. These latter are most useful. In this adrenal tumor the films show a normal sized and secreting kidney displaced downward by the mass above. In adrenal tumor, the mass is without the kidney. In Wilms's tumor, it will be in the kidney with calyceal and pelvic distortion. Cystoscopy and retrograde pyelography have been only rarely necessary to differentiate these tumors from other renal masses. The malignant nature of these tumors and their extreme blood vessel expansion present a situation too dangerous to delineate these tumors by retroperitoneal gas insufflation.

Avoidance of trauma to the tumor and early removal offer the only possible surgical correction. In these infants the wide, complete transperitoneal approach across the upper abdomen is, in our opinion, the better route of access. After deflection of the peritoneum over the vena cava and aorta, all vessels to and from the tumor are ligated and divided. This should be accomplished without tumor handling if possible, or with the least possible tumor handling, if necessary for exposure. Only after all possible vessels are separated should the tumor be delivered with all its fascial planes and attachments. In the few rare cases seen at the Babies Hospital that were discovered by accident and removed in this fashion we have seen patients remain free from recurrence. With tumor extension impossible to remove and with metastases, radiation has produced recession of the metastases but, as they receded, the tumor appeared elsewhere. There are fewer cancers with graver prognosis than the sympathicoblastomas of infancy, because the adrenal being higher than the kidney and more sheltered beneath the costal flare, they are more likely to escape early detection than Wilms's tumors.

Neurocytomas. More rarely are seen the tumors of ganglia cells occurring in the older age group. These relatively benign tumors also occur in any of the sympathetic ganglia as well as the adrenal. These tumors, mostly symptomless, are discovered by accident as a tumor mass. For differential diagnosis, secretory or retrograde urograms, gas insufflation x-rays, and angiograms may be used. The therapy is surgical removal. This has been successfully done through all approaches, flank, transthoracic and transperitoneal. They are well encapsulated, not greatly vascular and are removed without difficulty. Because most of these tumors are benign or of low grade malignancy, recurrence is less frequent if completely removed.

Pheochromocytoma. Tumors of the pheochrome cells of the sympathetic system are not frequent but are now of unusual interest because of the newer steps in diagnosis and in therapy. The tumors more frequently occur in the adrenal, estimated at about 80 per cent of the cases seen. Of the remaining, these occur mostly in the abdominal sympathetic ganglia and a few rare ones have been reported occurring in the thorax. They are sometimes multiple, estimated at 16 per cent, usually two being present and very rarely more. About 91 per cent of the cases are benign and 9 per cent reported as malignant. There has been an associated cutaneous neurofibromatosis with the tumor in 5 per cent of the cases and those often had multiple tumors. They occur in children but are more frequently seen in young adults and more often in women.

The secretion of the pheochrome cells of the adrenal have been identified as epinephrine and nor-epinephrine. When tumor occurs there is an excess secretion of these catechols and the symptoms depend upon the amount of each and also upon the intermittent or continuous release of the pressor substances into the blood. Assay of tumors shows that epinephrine has occurred anywhere from .95 mg. to 6.95 mg. per gram of tumor and nor-epinephrine has varied from .03 to 6.5 mg. per gram of tumor. The exact release mechanism of the pressor substance is not as yet clear but may be stimulated by many means.

The symptoms apparently depend upon the amount of these catechols released and present in the blood. It also appears that these catechols are also eliminated in the urine when in excess, and their presence and amount have been identified. The variable symptoms seen in different cases of these tumors apparently are accounted for by the variable amounts of the secretions. The effect of these two hormones vary. Excess epinephrine in the blood produces subjective symptoms, systolic hypertension mostly due to increased cardiac output, glycogenic changes in blood and urine, and hypermetabolism. Excess nor-epinephrine on the other hand produces hypertension because of increased peripheral resistance and a more sustained character, little or no glycogenic change, few subjective symptoms and little increase in cardiac output. Some of these tumors rarely produce any symptoms at all, although assay shows increased presence of the catechols. There is as yet no reason for the normal release mechanism not to function in these non-symptom tumors.

These tumors have occurred with the following syndromes:

1) An individual, symptom-free, in whom a tumor has been found on accidental examination at operation or at autopsy.

2) The adrenal sympathetic syndrome:

a) With a usual normal blood pressure with intervals of paroxysmal hypertension (30 per cent).

b) A more or less constant hypertension with paroxysmal rises or simulating an essential hypertension (70 per cent).

In establishing the diagnosis the following aids have been introduced:

Pharmacological release tests: 1) use of ordinary causation factors, such as the cold pressor test; 2) histamine; 3) mecholyl; 4) tetraethyl.

Pharmacologic, adrenolytic, or sympatholytic agents: 1) benzodioxane; 2) dibenamine; 3) regitine.

Of these, the pressor release mechanism with histamine introduced by Kvale has been used more frequently and its effects have been better known. It is especially useful in the paroxysmal type case and will precipitate an attack usually similar to the typical one.

Of the adrenolytic or sympatholytic agents, benzodioxane, introduced by Goldenberg and his co-workers, is especially useful in the more sustained hypertensive in which the drug has reduced the blood pressure in only tumor cases with an accuracy of 98 per cent or over.

Dibenamine, a marked sympatholytic agent, has been used mostly in therapy of operative preparations and because of its lasting and other effects has not been widely used in diagnosis.

Regitine, introduced by Grimson, has been used diagnostically as well as therapeutically and for the latter it appears to be the most effective of these drugs

Identification of excess pressor substance Previous efforts to establish a workable estimation as to the presence of excess epinephrine were not practical Ernould and Picard in 1931 showed a pressure substance in the blood during an attack by chemical methods Beer and Prinzmetal in 1937 established a similar result by pharmacological methods Recently the identification of excess pressure substances in the urine has been accomplished by Goldenberg and others

Once the presence of the tumor has been determined pharmacologically, the *situation of the tumor or tumors has been shown by plain x rays, urograms,* retroperitoneal gas insufflation, and by angiograms

Treatment The relief of the syndrome is by surgical removal of the tumor or tumors A large factor in the successful removal of these tumors has been the *planning of the procedure There have been several adrenolytic agents used in* the operative handling of these cases First was dibenamine and second regitine Dibenamine has been used in 5–7 mg doses per kilogram of body weight given in an infusion of 300 to 500 cc of saline administered slowly for one hour The *action of the drug is prolonged and has serious side effects, temporary hemi-*anesthesia and tetany have occurred It reduces the blood pressure dramatically for 24 to 72 hours Operative intervention has been usually in the latter part of the depressor effect because an operative diagnostic aid, the rise of blood pressure while handling the tumor, is eliminated if the depressor effect is complete Also after a severe fall in pressure, the fall may not be reversed by nor epinephrine Second has been regitine This has been used as a diagnostic aid, but its therapeutic adrenolytic effect is especially useful at operation Here it is given 0 16 mg per kilogram several hours before operation Its effect is not lasting and its abatement may allow the identification of the tumor by a pressure rise on handling and its rise controlled by the immediate resumption of regitine Also on removal of the tumor its effects disappear sufficiently rapidly so that nor epinephrine will be effective in a short time if needed

The anesthesia problem in these cases has been largely concerned with four important elements adequate relaxation, the possibility of pneumothorax, the physiological effect of the excessive secretion during the removal of the tumor, and the sudden circulatory depression which may occur after extirpation of the secreting mass Anoxia must be avoided Cyclopropane, chloroform, and ethyl chloride are unwise choices for anesthesia in these cases Three way intravenous drip is most advantageous 1) saline, glucose, or blood, 2) regitine, 3) norepinephrine—4 mg /1 liter, and the proper use of each may make the sustaining of pressure most gratifying

Because of the multiplicity of these tumors and because of the variability of their locations, the transverse upper abdominal transperitoneal incision offers the best approach to the removal of these tumors A generous incision is necessary No regitine should be given until the complete abdominal exploration is done, in order to identify the tumor or tumors As soon as pressure symptoms occur, then regitine is given. It has been more satisfactory when multiple tumors have been present to remove an extra-adrenal tumor first, because it is usually more accessible. Ligation of all vessels before handling the tumor is safer. Exposure of the left adrenal is made by incision of the retroperitoneal tissue above the splenic flexure and mobilizing the large intestine down into the abdomen. Opening of the retroperitoneal fascia above the upper pole of the left kidney discloses the tumor. After ligation of all blood supply the tumor is removed. Immediately the nor-epinephrine drip is given to sustain the pressure. Reparation of the retroperitoneal area is done and the wound closed completely. A similar procedure on the right with mobilization of the duodenum to the left and the hepatic flexure downward accomplishes the same exposure. These tumors may be very vascular and in some the extra-adrenal tumors between the vena cava and aorta have been difficult to eradicate. On removal of all excess pheochrome tumor tissue the pressure syndrome is cured.

About 8 per cent or so of these tumors have been shown to be malignant. When malignancy occurs, the hypertensive factor is seen early in the disease and then the pressor symptoms wane as the tumor grows and metastases occur. These malignant tumors metastasize most frequently to the lungs and liver and the death occurs with the cachexia of malignancy and often without any pressor syndromes in the later part of the disease. For awhile the occurrence of a second tumor in a patient with pressor syndrome was considered to be metastases of the larger tumor and such case identified as malignant. It is now considered that these multiple tumors are usually benign similar to the solitary tumors. Complete removal of a malignant tumor in its early phase offers the only hope of correction. Such must be rare. We have had none in our records in which removal was successful in a malignant tumor.

CORTICAL TUMORS

Tumors of adrenal cortical cells have been classified as follows:

1) Tumors with no recognizable hormonal changes in the patient.

2) Tumors with hormonal changes: a) adrenogenital, b) adrenocorticoid (Cushing's type), c) mixed, with both adrenogenital and adrenocorticoid hormonal changes.

Nonhormonal tumors of the adrenal cortex. These tumors are not infrequent. They have occurred more frequently in the fourth or fifth decades and occur in both sexes. They are silent in early growth. When recognized, they have usually been present for a considerable period of time. After growth has progressed to a considerable size, they then cause pain in the flank or in the side of abdomen in which the tumor is present. Often they had been studied by roentgen examination of the intestinal tract without discovery. Later with increasing size of the tumor, a mass is found on the affected side. The deep location of the adrenal gland and the slow growth of the tumor and its slowness of invasion of adjacent viscera often allow the tumor to grow extremely large before it is discovered. Frequently loss of weight, fatigue and diminution of appetite, and anemia may be present. These tumors are not tender. Occasionally, at the time of first recognition of the tumor, pulmonary metastases may be demonstrated by thoracic roentgenograms In others, in spite of the extraordinary large size of the tumor, no metastases seem to occur

The roentgen studies of these cases show a mass in the flank above the kidney and displacing of the kidney downward At times the tumor may project anterior to the kidney and its outline may be shown by the shadows of other viscera If a tumor is small it may be necessary to *outline its shape by perirenal insufflation* with gas Angiograms usually show the expanded vascularity separate from the adrenal In large and palpable tumors such procedures are often unnecessary Some of these tumors occur in accessory adrenal glands, either in the perirenal area, where they have been confused with tumors of the tail of the pancreas or in the pelvis where they were thought to be tumors of the ovary or broad ligament Most of these tumors, although well encapsulated, are malignant, and because of their silence and large growth, may suggest a poor prognosis

Surgical complete removal of the tumor is the only accepted therapy Because of their large size, those in the adrenal area lend themselves best to removal through a large incision combining the thoracic transdiaphragmatic approach and extending well down into the abdomen anteriorly The rib, usually the tenth, transects the x ray shadow of the tumor and offers the widest approach Since most of the blood vessel expansion is on the anterior mesial aspect of the tumor, the extension of the incision far down into the abdomen is necessary After separation of the retroperitoneal layer from the tumor, all the viscerae are displaced downward in order *to visualize the vessels to the tumor* On the right, the duodenum is displaced to the left to expose the vena cava and aorta and on the left the pancreas is displaced to the right because it usually overlies the vascular tree of the tumor The tumors are readily separated from the other fascial planes after the vascular tree is ligated and separated because of their encapsulation When the tumor grows anteriorly in front of the kidney and down into the abdomen the approach to the vascular pedicle is more direct with the transverse transperitoneal incision in the upper abdomen On the right, displacement of the duodenum and hepatic flexure of the colon, after separation of the posterior peritoneum, exposes the area of the vena cava and aorta and the vascular tumor pedicle is identified, ligated, and separated On the left, the splenic flexure is mobilized *and displaced downward exposing the tail of the pancreas and the* vessels with the tumor *as well as those to the left kidney* After ligation of the main vessels anteriorly, either associated with the aorta and cava or with the renal blood supply, the tumor usually is easily delivered except for separation of the phrenics high in the posterior cavity of the tumor area

Recovery after removal of these tumors is the rule, and as a surprisingly fair number of these patients have apparently no metastases, freedom from extension, metastases or recurrences is often an occurrence

Hormonal tumors of adrenal cortex Androgenic tumor with the symptoms of virilism occurs more often in younger individuals It occurs in children but is less frequent than bilateral adrenal hypertrophy When it occurs in children, the child has first been a normal one, then a change occurs toward adult masculinity

It occurs more often in the female child (in ratio 4 to 1). In the female there is clitoral hypertrophy, vaginal atrophy, pubic hair, acne and increased musculoskeletal development. In boys the signs of puberty occur without corresponding increase in size of the testes. Accompanying the changes, there occurs an elevation of the 17-ketosteroid estimation in the urine. The amount varies with the duration of symptoms and size of the tumor. Often there may be a marked increase in the urinary estrogens and this with no apparent clinical recognizable effect upon the patient. There may be little difference in appearance between a case of tumor and bilateral adrenal hypertrophy. A differential between these two conditions has been the observation that cortisone administered to an adrenal hypertrophy will reduce the 17-ketosteroids in the urine significantly, while on the contrary, cortisone given to a tumor case produces no reduction of the 17-ketosteroids.

Similar tumors are seen in older girls and in adult women. In these at the onset amenorrhea occurs with hirsutism. There then follows a recession of breasts and other female sex characteristics and a hypertrophy of male elements, particularly hair and the clitoris. The symptoms progress in severity with the increasing size of the tumor and assay levels of the 17-ketosteroids augment with the growth of the tumor. In tumor cases in adults the same phenomenon occurs with the administration of cortisone; there is no reduction in the assay levels of the 17-ketosteroids in the urine. The excretion of estrogens in the urine may be normal and may be elevated. There usually is no other deviation from the normal metabolism, in sugar levels, sodium and potassium levels nor in the corticoids.

Once the symptoms and assays have shown that there is present an independent adrenal androgenic excretion, the location of a tumor as a cause has been most successful with perirenal insufflation of gas. In these cases the fascial planes allow the gas to infiltrate easily and outline the adrenal and a tumor, if present, so that it is easily indentifiable. If the tumor is large it may displace the kidney downward and be so shown by pyelograms. If the vascular tree is large it may be shown by angiograms.

Practically all of the cases with only androgenic syndromes and no other metabolic changes have been shown to be due to benign adenomas of the adrenal and, in these, cure of the case is almost certain by operative removal. The operative removal is accompanied by no extra risk due to hormonal effects. These cases stand stress and trauma well, and there is no depression of function of the contralateral adrenal. These tumors may be removed successfully either through the flank, through a thoraco-abdominal incision or with a transverse abdominal transperitoneal approach. No special hormonal operative management is necessary. The tumors are very soft and cellular and are easily broken if handled. Recovery is the rule with complete reversal of the symptoms, except those that are fixed such as epiphyseal closure. In the women there is resumption of menses with loss of excess hair. As yet none of the female patients operated upon by us with androgenic tumor have subsequently become pregnant.

Tumors with excess estrogens are rare; less than twenty have been reported. They have occurred more often in adult males, less in children. They have been mostly carcinomas and have metastasized The symptoms are a decrease in male characteristics and an increase in the female sex characteristics, recession in the size of penis, loss of hair on chest and genitals, recurrence of scalp hair if bald, loss of sex desire, impotence and increase in size of nipples and breasts There may be some resemblance to the symptoms seen in testicular chorio epithelioma Large amounts of estrogens have been found in the urine with adrenal tumor, but no prolan, whereas in chorio epithelioma large amounts of prolan, the hormone of syncytial cells, are present A few of these estrogenic tumors were large and palpable, and were removed with cessation of symptoms but with recurrence of the symptoms and metastases of the tumor Gas insufflation roentgenograms have successfully located some of these tumors Removal has been accomplished by the flank, by thoraco abdominal approach or by transperitoneal routes They offer no problem in hormonal management at the time of operation

Tumors with excess corticoids The syndrome described by Cushing occurs with adrenal tumor as well as with bilateral adrenal hypertrophy Tumor, however, is much less often seen as a cause The tumors occur more frequently in adult females, less often in males and in children These cases show the rapid painful obesity of trunk-type with rounded "moon" face and "pigs eye" appearance Stria, skin changes and other metabolic changes occur caused by the effect of excess corticoids elaborated by the adrenal tumor These excess corticoids may be identified in the urine Usually there is a reduction of the 17 ketosteroids and of the estrogens in the urine

The diagnosis of adrenal hypercorticism is now not difficult with the recognition of the symptoms and of the various tests which show the metabolic changes Whether tumor or bilateral adrenal hypertrophy is present as the cause of the syndrome is most important We have consistently used bilateral perirenal gas insufflation x rays to determine the difference These have not been so satisfactory as those seen with adrenogenital syndrome, due to the increased deposits of fat in the perirenal area However, when tumor has been present it has always been outlined by the gas and recognized Also recognition of the tumor has simplified the proceedings We have used angiograms for the location of these tumors but to date they have been less helpful than the gas insufflation If tumor cannot be localized by x ray and it is suspected, it may be necessary to do a bilateral adrenal exploration Finding the tumor by x-ray localizes the side and place and reduces the operative exposure to one adrenal

In contrast to the surgical therapy of the uncomplicated adrenogenital syndrome tumor case, operative correction of an adrenal tumor with the corticoid syndrome is a serious risk to the patient The incidence of severe postoperative reaction following removal of the tumor in this type of case is frequent and fatal unless steps are taken to correct the expected Addisonian crisis The excess corticoids produced by the tumor depress the activity of the contralateral adrenal and this Addisonian crisis will occur unless substitution therapy is given before, during, and after operative removal of the tumor and should be carried on until the opposite adrenal resumes function This may be from one to six weeks The therapy consists of the administration of cortisone and ACTH for 2 days before operation, then cortisone, ACTH, desoxycortisone and salt during operation and for 2 days postoperatively. The desoxycortisone and the cortisone dosage is then lowered and if no evidence of adrenal failure is present, only ACTH and saline are administered. The desired idea is to carry the substitution hormones through the dangerous period while stimulating the depressed contralateral adrenal to resume function rapidly under the effect of the ACTH. These patients are poor risks for infections and stress.

Removal of tumors with corticoid syndromes has been successful through the flank, through thoraco-abdominal approach and through the transperitoneal route. Most of these tumors are benign and have not been very large. They are vascular, soft, easily fragmented and are enucleated without difficulty. Often they may be resected from normal appearing adrenal tissue. If there is a successful recovery from the adrenalectomy, recession of the symptoms rapidly occurs to normal. We have seen recovery in women to normal and later followed by pregnancy and the delivery of a normal child.

Mixed syndrome tumors: At times, in all age groups, syndromes resembling Cushing's disease and with other symptoms of virilism are seen. These again are more frequently seen in the female. Most all of these mixed syndrome cases have been shown to be due to carcinoma of the adrenal cortex.

In children the signs of virilism appear with hirsutism, sexual precocity, and with changes in the musculoskeletal system. Frequently when examined they have shown some hypertension and glycosuria. Studies on these children have shown marked excretion of 17-ketosteroids in the urine. These 17-ketosteroids are fixed against cortisone depression. Chemical studies show some of the changes in metabolism as seen in Cushing's disease. Most of these cases have shown rapid expansion of the tumor so that a mass is often palpable. These cases also show renal displacement by the mass expansion. Metastases may be disclosed on examination. In adults a similar phenomenon is noticed. The main suggestion may be that the cause is marked corticoid changes resembling Cushing's and with moderate genital changes of hirsutism and clitoral hypertrophy with the amenorrhea; again, as we have recently seen, a marked corticoid syndrome in a male but with no sexual regression and a very marked elevation of the 17-ketosteroids in his urine that were also fixed against cortisone. Others may show an adrenogenital syndrome well marked with sexual changes and with well-marked hypertension, glycosuria, some fat and skin disturbances as stria. These all, in our experience, have been due to carcinoma of the cortex. Most of these mixed tumor syndromes in adults have been rapidly growing large tumors, and the demonstration of the tumor by palpation, by x-ray pyelograms, gas insufflation x-rays and angiograms has not been difficult.

Operative procedures on such cases require the same preparation as for tumors with corticoid syndromes: hormonal preparation before, during, and after operation. The widest possible approach should be used to prevent handling of the tumor because of malignancy. Transverse upper abdominal transperitoneal approach has been better for tumor extension into the abdomen. The vascular supply to these tumors is greatly expanded and the vessels are friable. Ligation often is difficult unless fat tissue is included with the ligature When the tumor is high in the curve of the diaphragm, the thoraco abdominal approach is better The rib removed should be the one across the main upper part of the tumor, usually to the tenth All effort should be made to ligate and sever the vascular pedicle or supply with a minimum of handling the tumor The tumors often do not come out easily and vascular areas to the renal vessels and to the phrenic may be tedious to control

On recovery, blood restoration is essential as well as substitution hormone therapy Adrenal depletion symptoms may occur Cases have recovered spontaneously in the past due to corticoid secretion by metastases Recovery of this type of tumor with return to normal and without recurrence is the rarest of the various cortical malignancies Early recognition is needed to remove these malignant adrenals before metastases because they have a high degree of radiation resistance It has been possible to determine the spread of metastases by the augmenting amount of 17-ketosteroids in the urine Hypophysectomy has had no influence on the hormonal excretion in the rare cases in which it has been tried

SUMMARY

A review of the various tumors of the adrenal is presented with a short description of the origins, symptoms, operative handling problems and the operative approaches which, with some technical aspects, experience has shown to be the more satisfactory A discussion is presented of the handling of the hormonal problems incident to the removal of these tumors

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BLOOD PHENOL IN RENAL INSUFFICIENCY

HERBERT L. WARRES

From the Department of Urology, Presbyterian Hospital of Philadelphia, Pa.

Uremia is "a complex auto-intoxication, the variegated clinical picture being the summation of the effect of retention of various urinary constituents." (Fishberg.) That urea is not the causative agent of symptoms of uremia is borne out in everyday clinical evidence. Virtually every known urinary constituent at one time or another has been indicated as an etiological factor. No single factor is a prime agent. Of the various retention products, however, certain ones seem to play the more important role.

Becher demonstrated indican, phenol, p-cresol, diphenol, and other aromatic oxyacids in uremic blood. He later concluded that phenol, especially free phenol, was directly responsible for uremic symptoms. This was verified by Marcolongo, Harrison, and Mason. More recently Dickes concluded: 1) The degree of cerebral depression in uremic patients shows a direct correlation with the height of the phenolic blood level. 2) The total phenols appear to have a greater correlation with the degree of depression than do the free or conjugated phenols. 3) The blood level of the total phenols shows better correlation with the degree of cerebral depression than does the urea nitrogen. 4) The free phenols do not account for the unidentified acid radicals in renal acidosis. 5) High phenol levels have a grave prognostic import. 6) Patients who have a phenol level above 3.90 total, 2.90 free, 1.01 conjugated, in his experience, do not recover.

Raab postulates that catechol and phenol compounds are the main cause for the electrocardiographic changes and physical signs of cardiac failure in uremic patients. Mason attributes gastro-intestinal symptoms to retention of urea with the formation of ammonium salts by intestinal bacterial decomposition, guanidine intoxication which in itself produces gastro-enteritis, and dehydration and acid-base imbalance which are secondary factors. He ascribes respiratory symptoms to guanidine and acidosis. Mason believes that nervous manifestations are due to two antagonistic influences: a deficit of calcium ions in the cerebrospinal fluid from the retention of phosphate ions causing irritation and an elevation of the cerebrospinal fluid phenol level producing narcotic effect. Complicating this is retention of guanidine which can be either irritative or depressive depending upon the level.

Roen states that previous methods for determining blood phenol are nonspecific. Becher employed the Jolle reaction, method of Benedict and Theiss, and method of Folin and Denis. These procedures determine not only phenol but also substances with phenol grouping as p-cresol, diphenol, indican, skatol, and indole. Harrison and Mason used the method of Rakestraw which measures not only phenol but many similar substances. Dickes used the method of Theiss

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and Benedict. Roen employed the method of Bernhart based on the Millon reaction which is highly specific for phenol structure, has high accuracy, great specificity, and an error of 3 per cent or less.

Our studies have been divided into two phases. First, the method of Bernhart has been briefly investigated. Second, blood phenol levels were obtained in 58 patients and an attempt made to correlate these with clinical symptoms, blood urea nitrogen, blood creatinine, and other renal function tests. In several patients liver function tests were also made.

Our most important finding in the investigation of the method of Bernhart was the necessity of using fresh sodium nitrite solution. In recovery studies, more than 20 per cent difference was noted between use of stock and freshly prepared solutions. Our recovery studies then averaged 92 per cent.

The ages of our patients ranged from 11 years to 91, the average being 56.6 years. Forty-two were males, 16 females. Forty-three were white, 15 Negroes. These patients will be considered in five groups.

Group 1 was composed of 17 patients, all of whom had normal blood urea nitrogen levels on admission and during the period of study. (See table 1.) For the purposes of this study, these were considered the control group. The pathological changes requiring hospitalization of these patients would place nine in the pre-renal group, three in the renal and five post-renal. Blood urea nitrogen levels varied from 8 to 16, average 12.6. Blood phenol levels ranged from 0.05 to 2.80, average 0.59. Creatinine blood levels were determined in 9 of these patients and varied from 0.6 to 2.6, average 1.63. Blood urea clearance tests, done on 4 patients, ranged from 58 per cent to 80 per cent. Fishberg urine concentration test, done in 2 cases, was normal in one and showed a fixed specific gravity in the other (cases 31, 57, table 1). A phenolsulphonthalein test was done in 4 cases and showed moderate renal impairment in two (cases 28, 57, table 1). This test was done as follows:

A catheter was inserted into the bladder and the bladder emptied. One cubic centimeter of the dye was injected intravenously. Urine was collected as three 20 minute samples for a total of 1 hour. Results in case 28 were 13 per cent, 30 per cent, and 7 per cent for a total of 50 per cent. Results in case 57 were 3 per cent, 18 per cent, and 6 per cent for a total of 27 per cent.

One patient of this group had an elevated blood phenol level (2.8). He entered with symptoms of prostatism and was found to have adenocarcinoma of the prostate. *Retrograde pyelography revealed essentially normal kidneys.* The blood urea nitrogen was 11, creatinine 2.1, and phenol 2.8. Neither he nor the other patients of this group showed uremic symptoms.

Total blood proteins, albumin-globulin ratio was determined in 5 patients and were normal in each. Liver function studies were done in 2 cases and disclosed mild hepatic damage (table 6). All 17 patients recovered sufficiently to leave the hospital.

Group 2: Three patients had elevated blood urea nitrogen levels during the period of study which returned to normal by the time the blood phenol was determined (table 2). Only one of these presented uremic symptoms (1+). Symptoms were classified as follows: The patient was regarded as retarded (1+)

when his reaction time to questions was noticeably slow and he had no desire to be up and about. The drowsy patient (2+) was one who was sleepy and inclined to doze most of the time. In semicoma (3+), the patient was stuporous but could still be aroused. In coma (4+), the patient could not be aroused. One patient (case 48) entered in acute urinary retention secondary to benign prostatic hypertrophy. In addition a history of alcoholism was obtained. On admission the blood urea nitrogen level was 19. Following prostatectomy, the patient became confused, somewhat disoriented, and had a blood urea nitrogen level of 41. Blood phenol was not obtained until 2 days later when these symptoms had disappeared. At that time the blood urea nitrogen level was 12 and blood phenol 0.09.

TABLE 1. *Group 1. Blood phenol determinations in patients having a normal blood urea nitrogen level on admission and during the period of study*

CASE	BUN	CREATININE	PHENOL	UREA CLEARANCE	CHLORIDES	DISEASE
				%		
3	13	1.1	0.10	—	620	Rt. hydronephrosis
7	8	—	0.07	—	—	Median bar
9	11	2.1	2.80	—	550	Carcinoma of prostate
15	9	0.6	0.56	—	—	Neurogenic bladder, diabetes, infectious hepatitis
16	16	—	0.56	—	—	Diabetes
17	13	—	0.07	—	—	Prostatic hypertrophy
18	15	1.5	0.08	—	—	Adenocarcinoma of sigmoid colon
19	11	2.6	1.30	80	—	Essential hypertension
25	15	1.6	0.09	58	—	Essential hypertension
28	13	—	2.00	—	—	Prostatic hypertrophy
31	16	2.2	0.80	78	—	Hypertensive cardiovascular disease
36	9	—	0.10	—	—	Rt. pyelonephritis
37	16	—	0.09	—	600	Prostatitis
41	14	—	1.20	—	660	Rt. pyelonephritis
44	9	1.2	0.08	—	600	Toxemia of pregnancy
53	10	—	0.09	—	690	Carcinoma of cervix
57	16	2.0	0.05	73	—	Essential hypertension

TABLE 2. *Group 2. Patients with elevated blood urea nitrogen levels on admission which had returned to normal at the time blood phenol was determined*

CASE	DATE	BUN	CREATININE	PHENOL	UREA CLEARANCE	DISEASE
10	4/13	39	—	—	—	Pulmonary embolus
	4/15	13	1.2	0.72	—	
29	1/1	49	—	—	—	Bleeding duodenal ulcer
	1/6	10	1.1	0.05	71%	
48	2/7	19	—	—	—	Prostatic hypertrophy
	2/9	41	—	—	—	
	2/11	12	1.4	0.09	—	

The remaining 38 cases had elevation of the blood urea nitrogen level at the time blood phenol determinations were made. The pathological changes would place 21 in the pre-renal classification, 8 in the renal and 9 in the post-renal. These will be discussed separately.

Group 3: In the pre-renal group (table 3) blood urea nitrogen levels at the time blood phenol was determined varied from 176 to 9, average 52.3. Blood creatinine levels ranged from 0.1 to 11.3, average 2.7. Blood phenols ranged from 0.03 to 5.9, average 1.52. Urea clearance tests were performed in 5 cases and varied from 75 to 40 per cent. The latter determination (40 per cent) was done after the blood urea nitrogen level had dropped from 50 to 9. Carbon-dioxide combining power was ascertained in 5 cases and varied from 45 to 34. Blood chlorides were determined in 8 cases and varied from 440 to 650. Total protein, albumin globulin ratios were obtained in 3 (cases 47′, 52 and 55) and were normal in each. Phenolsulphonthalein tests were performed in two: Case 47′ results were 20 per cent, 15 per cent and 5 per cent for a total of 40 per cent in 1 hour; case 55, 0 per cent, 25 per cent and 20 per cent for a total of 45 per cent. Liver function studies were done in 3 patients, one having been investigated during two separate hospital admissions (cases 21, 47′, 47″, 52) and showed mild liver damage in each. (See table 6.)

Seven of these patients displayed no symptoms of uremia. Blood phenol levels ranged from 0.09 to 2.3, average 1.27. Fourteen patients exhibited symptoms clinically resembling those seen in uremia. Symptoms in these were graded from 1+ to 4+. Blood phenols varied from 0.03 to 5.9, average 1.78. It is interesting to note that case 47 presented 3+ uremic symptoms during his first admission with a blood phenol level of 1.4 and no uremic symptoms at a later admission with a blood phenol level of 2.3. With this exception, all patients having a blood phenol level above 2.1 demonstrated uremic-like symptoms. But not all patients with these symptoms had an elevated blood phenol level. It must be remembered that pre-renal disease may produce an elevation of the blood urea nitrogen level and symptoms similar to those of uremia without true uremia being present. Therefore, the renal and post-renal groups are of most importance in this study.

Group 4: The blood urea nitrogen levels determined concomitantly with that of blood phenol in the renal group, varied from 330 to 22, average 94.7. (See table 4.) Twenty-one joint creatinine blood phenol determinations were made. Creatinine levels varied from 18.0 to 1.4, average 7.8. Carbon-dioxide combining power was determined in 4 cases and ranged from 21 to 48, average 38. Urea clearance values were obtained in 2 cases and were 41 per cent and 59 per cent. Eleven blood chloride determinations were made in 3 cases and ranged from 400 to 610, average 530. Phenolsulphonthalein tests were performed on 2 patients: Results in case 11 were >5 per cent, >5 per cent, >5 per cent for a total of 10 per cent in 1 hour; case 24, 3 per cent in 1 hour. Fishberg concentration test was done in case 46 and showed a fixed specific gravity. Blood potassium in case 58 was 6.7 mEq. Total protein, albumin-globulin ratio was normal in case 42. Of the twenty-three blood phenol determinations made, levels ranged from 0.08 to 6.1, average 3.09. Uremic symptoms ranged from 0 to 4+. All patients having a blood phenol level of over 2.1 exhibited such symptoms. But not all patients

TABLE 3. *Group 3. Pre-renal group having an elevated blood urea level at time blood phenol was determined. First blood urea nitrogen level listed in each case done at or shortly after admission*

CASE	DATE	BUN	CREATININE	PHENOL	UREA CLEARANCE	CO_2	CHLORIDES	UREMIC SYMPTOMS	DISEASE	R/D*
					%					
1	3/28	81	—	—	—	—	—	—	Myocardial infarction	D
	4/9	79	5.1	4.2	57	—	—	2+		
2	4/6	33	—	—	—	—	—	—	Anxiety neurosis	R
	4/9	41	3.0	1.3	—	—	—	0		
6	3/1	61	—	—	—	—	—	—	Gastric carcinoma	D
	3/3	82	8.3	5.9	—	—	—	4+		
8	1/26	41	—	—	—	—	—	—	Myocardial infarction	D
	1/27	68	6.4	3.8	—	—	—	4+		
14	2/21	49	—	—	—	—	—	—	Carcinoma of bronchus	D
	2/25	24	1.3	0.8	—	—	—	0		
20	6/19	20	—	—	—	—	—	—	Peritonitis	D
	8/2	29	0.9	0.06	—	45	650	4+		
21	1/19	21	—	—	—	—	—	—	Intestinal obstruction	D
	1/27	60	1.6	0.04	—	—	—	2+		
22	2/7	50	—	—	—	—	—	—	Myocardial infarction	R
	2/9	28	1.8	1.2	—	—	—	0		
23	12/16	13	—	—	—	—	—	—	Carcinoma of colon	R
	1/10	26	0.1	0.06	—	—	470	0		
26	1/21	48	1.1	0.9	—	—	—	3+	Lobar pneumonia	R
30	4/7	70	—	—	—	—	—	—	Cholecystitis	R
	4/8	35	2.6	3.1	—	—	—	3+		
38	2/9	10	—	—	—	—	—	—	Carcinoma of rectum	R
	2/23	25	1.2	1.2	75	—	—	0		
39	3/21	16	—	1.1	—	—	460	3+	Diabetic acidosis	D
	3/30	62	2.4	1.3	—	—	—	3+		
43	1/17	44	—	—	—	—	—	—	Myocardial infarction	D
	1/21	51	2.2	1.4	—	39	550	3+		
45	3/15	35	1.1	2.1	—	35	—	4+	Cerebral hemorrhage	D
47′	7/19	21	—	—	—	—	—	—	Toxic hepatitis and prostatic carcinoma	R
	8/10	176	9.8	1.4	—	34	500	3+		
	8/12	160	11.3	1.2	—	41	440	3+		
47″	2/23	50	1.7	2.3	61	—	—	0	Cholecystitis and prostatic carcinoma	R
	3/24	32	2.2	2.3	—	—	—	0		
49	12/19	52	—	—	—	—	—	—	Addison's disease	D
	12/21	45	1.3	1.1	—	41	450	1+		
51	1/14	14	—	—	—	—	—	—	Myocardial infarction	R
	1/22	55	1.5	1.0	—	—	—	0		
52	5/4	10	—	—	—	—	—	—	Intestinal obstruction	R
	5/10	41	2.8	0.03	—	—	610	1+		
55	12/15	14	—	—	—	—	—	—	Cholecystitis	R
	12/21	35	1.2	0.09	51	—	—	0		
56	12/21	50	1.1	1.0	—	—	550	1+	Intestinal obstruction	R
	12/28	9	1.7	0.8	40	—	—	0		

* Recovered or died.

demonstrating uremic symptoms had an elevated blood phenol. In those patients having a significantly elevated blood phenol, there was no correlation between the degree of symptoms and the blood phenol level. Case 27 with the highest phenol level in this series (6.1) showed few uremic symptoms (1+). There was no correlation between the height of the blood phenol and prognosis.

TABLE 4. *Group 4. Renal group showing an elevated blood urea nitrogen level at time of blood phenol determination. First blood urea nitrogen level listed in each case done at or shortly after admission*

CASE	DATE	BUN	CREATININE	PHENOL	UREA CLEARANCE	CO$_2$	CHLORIDES	UREMIC SYMPTOMS	DISEASE	R/D*
					%					
4	1/17	13	—	—	—	—	—	—	Oliguria following bilateral nephrolithotomy	R
	1/24	75	8.9	4.1	—	28	540	3+		
	1/26	80	6.8	3.4	—	39	520	2+		
	1/27	100	7.3	4.3	—	39	570	2+		
	1/29	100	8.1	5.1	—	42	590	2+		
	2/2	27	2.1	2.3	—	43	600	1+		
	2/5	22	1.5	1.3	—	39	580	0		
11	1/13	30	—	—	—	—	—	—	Malignant nephrosclerosis	D
	1/14	30	6.0	1.3	—	—	—	1+		
24	2/11	65	5.1	0.08	—	—	—	1+	Malignant nephrosclerosis	R
	2/14	60	8.2	1.2	41	—	—	2+		
	2/16	58	5.2	1.0	—	—	—	2+		
27	1/4	92	—	—	—	—	—	—	Anuria due to toxic nephrosis	R
	1/5	105	12.2	2.3	—	—	440	0		
	1/7	93	14.0	3.8	—	—	540	1+		
	1/10	105	17.0	5.6	—	48	410	1+		
	1/12	100	18.0	6.1	—	—	610	1+		
	1/13	100	16.5	5.9	—	—	—	1+		
	1/20	59	3.0	4.1	—	—	—	0		
	1/22	31	1.4	1.8	—	—	—	0		
	1/24	27	2.3	1.3	—	—	—	0		
42	4/2	40	—	—	—	—	—	—	Glomerulonephritis, nephrotic stage	D
	4/9	39	2.1	1.1	—	—	—	1+		
46	1/6	63	7.8	2.8	59	—	—	2+	Chronic glomerulonephritis	R
54	7/19	212	—	—	—	—	—	—	Malignant nephrosclerosis	D
	7/22	310	—	4.1	—	21	—	1+		
	7/26	330	15.4	3.95	—	—	—	3+		
58	1/17	228	—	—	—	—	—	—	Sulfonamide anuria	D
	1/28	199	—	4.28	—	48	400	4+		

* R/D—recovered or died.

Group 5: Blood urea nitrogen levels determined concomitantly with that of the blood phenol in the post-renal group ranged from 250 to 10, average 67. (See table 5.) Ranges in the 15 creatinine determinations were 7.0 to 1.1, average 3.6. Ranges in the 7 carbon-dioxide combining power determinations were 19 to 41, average 31.4. Urea clearance values were obtained in 4 cases. Ranges were 51 to 84 per cent, average 61.6 per cent. Chlorides in 6 cases ranged from 640 to 520, average 594. Phenolsulphonthalein tests were performed on 5 patients.

Results were: Case 40, 0 per cent, 23 per cent, and 8 per cent for a total of 31 per cent in 1 hour. Cases 12 and 50, 1 per cent in 1 hour. Case 13, 0 per cent in 1 hour. Case 34, 0 per cent, 3 per cent and 1 per cent for a total of 4 per cent. A total protein, albumin-globulin ratio was procured in case 33 and was normal.

TABLE 5. *Group 5. Post-renal group showing an elevated blood urea nitrogen level at time of blood phenol determination. First blood urea nitrogen level listed in each case done at or shortly after admission*

CASE	DATE	BUN	CREATININE	PHENOL	UREA CLEARANCE	CO_2	CHLORIDES	UREMIC SYMPTOMS	DISEASE	R/D*
					%					
5	12/19	33	—	—	—	—	—	—	Neuroblastoma of prostate	D
	12/22	40	6.8	3.1	53	—	—	1+		
	12/29	—	4.5	1.1	54	—	—	1+		
12	10/30	66	—	—	—	—	—	—	Prostatic hypertrophy	R
	11/8	51	—	0.85	—	—	—	1+		
	11/24	80	—	5.80	—	—	—	2+		
	12/8	55	—	4.10	—	—	—	2+		
13	7/26	216	—	2.90	—	19	580	1+	Prostatic hypertrophy	D
	7/29	250	6.2	3.0	—	—	—	1+	Prostatic hypertrophy	D
	7/30	200	—	2.98	—	—	—	1+		
	7/31	128	5.0	2.3	—	—	—	1+		
	8/2	96	2.2	2.1	—	—	—	0		
32	7/28	22	—	0.5	—	—	640	2+	Prostatic hypertrophy	D
33	1/5	13	—	—	—	—	—		Hydronephrosis secondary to ureterocolic transplant	R
	2/8	25	1.9	0.08	—	—	580	1+		
	3/1	42	1.7	1.2	—	—	—	0		
34	8/7	12	—	0.08	84	35	620	0	Prostatic carcinoma	D
	12/1	31	—	1.3	—	—	—	0		
35	3/18	54	—	—	—	—	—	—	Prostatic hypertrophy	R
	3/19	33	1.9	0.9	—	—	—	2+		
	3/21	42	2.5	1.0	54	31	520	2+		
	3/23	35	—	1.3	—	28	—	2+		
	3/28	31	—	1.2	—	—	—	2+		
	4/9	31	4.2	0.9	—	—	610	2+		
40	4/6	11	—	—	—	—	—	—	Anuria following ureterocolic transplant	D
	4/15	47	7.0	3.1	—	28	600	1+		
	4/19	52	3.4	1.9	—	39	600	0		
	4/23	21	2.8	1.6	—	41	600	0		
50	2/1	10	3.1	1.3	74	—	—	0	Prostatic hypertrophy	R
	2/7	59	1.1	1.9	—	—	—	0		

* R/D—recovered or died.

Ranges of the 25 blood phenol levels obtained were 0.08 to 5.80, average 1.86. Uremic symptoms ranged from 0 to 2+. Every patient having a blood phenol of over 2.1 exhibited some uremic symptoms although occasionally only a mild degree. Not all patients with uremic symptoms had an elevated phenol. There was no parallelism between the height of the blood phenol and the degree of symptoms There was no correlation between the blood phenol level and prognosis

TABLE 6 *Liver function tests Bil —bilirubin Chol/Ester—cholesterol/cholesterol esters T prot, A/G—total protein, albumin globulin ratio BSP—percentage bromsulphthalein retention Ceph —cephalin flocculation Misc —miscellaneous*

CASE	PHENOL	BIL.	CHOL/ESTER	T PROT, A/G	BSP	CEPH	MISC
2	1 3	0 9	—	8 0	—	—	4 1 lipase
15	0 56	0 47	185/125	9 0(5 5/3 5)	0	0	13 2 alk phosphatase
21	0 04	3 7	—	—	—	—	—
24	1 0	—	152/74	—	—	—	—
25	0 09	—	179/68	7 2(4 2/3 0)	40	1+	—
42	1 1	—	261	7 1(4 1/3 0)	—	—	—
47′	1 4	4 4	—	6 5(4 1/2 1)	0	0	10 4 alk phosphatase
47′	1 7	3 8	—	—	0	0	121 amylase
52	0 03	0 17	—	—	—	0	41 amylase

DISCUSSION

There are two sources of blood phenol A portion comes from the physiological metabolism of the amino-acids phenylalanine and tyrosine (Dubin, Shambaugh) Another portion is derived from colon bacilli showing great hydrolytic activity toward proteins (Peters and Van Slyke) Wallace indicates that Clostridium sporogenes and Proteus vulgaris meet these requirements

Free phenols, being poisonous, are detoxified in the liver by conjugation with sulfuric or organic acids (Folin and Denis, Pelkau and Whipple) The conjugation of phenols has been used as a liver function test (Foster and Kahn) Comparison of blood phenol levels with liver function was not a primary aim of our study Yet the highest blood phenol value was obtained in a patient having definite liver damage (case 27) This patient had anuria secondary to toxic nephrosis resulting from carbon tetrachloride poisoning During the height of the disease the liver was palpable almost to the iliac crest Unfortunately liver function tests were neglected in this patient Two patients having elevated serum bilirubin values had normal blood phenol concentrations at that time (cases 21, 47′, 47″) One patient showing liver impairment by bromsulphthalein test had a normal blood phenol level The relationship of liver function to blood phenol values is worthy of additional study

Prior to the test of Bernhart for blood phenol, its measurement as a diagnostic criterion of uremia was considered unreliable since former tests were not specific Becher himself noted increases in pernicious anemia, gangrene of the lung, and cirrhosis of the liver The clinical investigations of Roen and Nesbit are the most important using this newer method

Roen studied 37 cases with an elevated blood urea nitrogen level and found none with symptoms of uremia without having an elevation of the blood phenol However, there was no correlation between the height of the blood phenol and the intensity of uremic symptoms Roen believed that the intensity of uremic symptoms depended upon the abruptness of rise in blood phenol He also demonstrated that the rise in blood phenol was not a terminal state and was reversible

Nesbit studied 25 cases and found that uremic symptoms, while frequently present, were not always related to an elevated blood phenol. This applied not only to uremic symptoms in general but to symptoms of narcosis in particular. He found no parallelism between the intensity of uremic symptoms and the level of blood phenol. There was no correlation between the blood levels of urea and phenol. Nesbit, too, pointed out that elevation of blood phenol is reversible.

In our study of 58 patients, all having a blood phenol level above 2.1 mg., had uremic symptoms with one exception. Many of our patients had symptoms which we interpreted as possibly due to uremia without having an elevation in blood phenol. This applied to all groups, pre-renal, renal, and post-renal. Elevation of blood phenol was a reversible process. The height of the blood phenol concentration had no prognostic significance.

With the one exception already mentioned, no patient having an elevated blood phenol value had a normal blood urea nitrogen level. There was no correlation between the height of the blood urea nitrogen and that of the blood phenol.

Only one patient had a raised blood phenol level and normal creatinine, as noted above. Not all patients having an elevation of blood creatinine showed an increased phenol. In general, the height of the creatinine was proportionate to that of the phenol. This was not always true as can be seen by two glaring exceptions: case 47′, creatinine 11.3, phenol 1.2; case 24, creatinine 8.2, phenol 1.2. Both patients had uremic symptoms. Blood phenol values tended to rise more slowly and decrease more rapidly than that of creatinine. This was not always true. In case 27 the blood creatinine decreased more rapidly than the phenol. There was no parallelism between the height of blood phenol and intensity of uremic symptoms. Creatinine levels, being more labile, were elevated in most patients showing uremic-like symptoms. There was no correlation between the height of creatinine levels and the intensity of uremic symptoms. Creatinine values, however, corresponded more closely with the degree of symptoms than did those of phenol.

Where these determinations were made, all patients having an elevated blood phenol had a decreased carbon-dioxide combining power. Not all patients having low carbon-dioxide combining power values had a raised blood phenol level. In the few cases where urea clearance was determined, patients showing an increased blood phenol concentration had a decreased urea clearance. The same was true where phenolsulphonthalein tests were done. No correlation existed between blood phenol and chlorides.

We wish to express our appreciation of an indebtedness to Miss Kathleen A. Rastatter, B.S., B. O. Chemist, head technician of the laboratories, Presbyterian Hospital.

SUMMARY

Fifty-eight patients were studied. With one exception, all having an elevation of the blood phenol had uremic symptoms. However, not all showing such symptoms had an increased blood phenol level. There was no parallelism between the intensity of uremic symptoms and the height of the blood phenol level. Elevation of the blood phenol was a reversible process and had no prognostic significance.

There was no correlation between the blood urea nitrogen and phenol levels In general, creatinine and phenol values were proportionate although not always so Creatinine corresponded more closely than the phenol levels in indicating patients presenting uremic symptoms

CONCLUSIONS

Patients representing an elevation of blood phenol show symptoms of uremia The reverse is not necessarily true

No parallelism occurs between the intensity of uremic symptoms and the blood level of phenol

Increase in the blood phenol concentration is reversible and has no prognostic significance

There is no correlation between the blood levels of phenol and urea

The blood levels of phenol and creatinine are proportionate in general

Creatinine is the better test for assessing the degree of renal insufficiency

Thompson, Brumm and Knepper Clinic, St Joseph, Mo

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RENAL THROMBOSIS

HORACE V. MUNGER

Two cases of renal thrombosis are presented to re-emphasize the differences between arterial and venous infarction of massive degree and less extensive infarction resulting from sclerotic and inflammatory changes.

In 1944 Melick and Vitt[1] reported a case of venous thrombosis in which early retrograde pyelograms were obtained, the first reported instance in which retrograde pyelograms were obtained as an early procedure in the course of the disease. Four years later Regan and Crabtree[2] presented a comprehensive study of this subject before the American Urological Association's annual meeting. They reviewed the literature to date and reported 90 cases adding four of their own. We are indebted to them for a concise detailed clinical differentiation between sterile arterial and venous thrombosis (tables 1 and 2).

Localized infarction resulting from involvement of the lesser branches of the renal arterial tree will result in smaller areas of necrosis; however, complete loss of function results as has been demonstrated by excretion urograms. Venous thrombosis within the cortex may result from primary hematogenous pyelonephritis and may by extension involve the renal vein.

It has been demonstrated·that infarction resulting from occlusion of the smaller vessels of the kidney will produce hypertension more promptly than will total infarction of the organ. The reappearance of function which may occur after occlusion of one of the major arteries does not so readily occur in smaller vessel occlusion due to the lack of collateral circulation. It seems obvious then that nephrectomy should be considered in these instances where severe cardiovascular disease does not preclude operative intervention.

Recently 2 cases of renal thrombosis have been observed. Presentation of them is made at this time.

CASE REPORTS

Case 1. Mrs. L. C., a 65 year old white housewife, was admitted to the Lincoln General Hospital on October 5, 1951, by her internist. She gave a 3 weeks' history of moderate substernal pain with a sensation that her heart was racing, this being accompanied by dyspnea. Five hours prior to admission she experienced rather severe precordial pain with associated palpitation.

The past history revealed mild rheumatic heart disease in childhood with no known sequelae. Uterine fibroids were removed in 1937. Rheumatoid arthritis existed during the past 5 years.

Physical examination showed cardiac enlargement; there were no demonstrable murmurs. The blood pressure was 110/64, pulse irregularly irregular. There was

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Read at annual meeting, South Central Section, American Urological Association, Hot Springs, Ark., October 1, 1952.

[1] Melick, W. F. and Vitt, A. E.: Thrombosis of the renal vein. J. Urol., 51: 587–596, 1944.

[2] Regan, F. C. and Crabtree, E. G.: Renal infarction: A clinical and possible surgical entity. J. Urol., 59: 981–1014, 1948.

a well-healed midline abdominal operative scar and moderate arthritic changes of the phalanges The remainder of the physical examination was normal

The patient was given Demerol and remained comfortable for several hours Chest x-ray revealed a markedly enlarged heart and the electrocardiogram revealed auricular fibrillation Urinalysis of a clean voided specimen: clear straw, specific gravity 1 020, no albumin, sugar or acetone, 2–4 white blood cells per high power field on microscopic examination Blood count: 90 per cent hemoglobin, 4,080,000 red blood cells, 9,100 white blood cells, differential, normal The second hospital day quinidine therapy was begun The cardiac rhythm became normal and the rate dropped to the 70–80 per minute range The patient was apparently symptom free beginning with this day A second electrocardiogram taken on the third hospital day revealed a normal sinus pattern but evidence of auricular enlargement and of myocardial damage had appeared

TABLE 1

1 Sudden onset of flank or upper abdominal pain
2 Nonfunctioning kidney shown by urograms and excretion tests
3 Normal retrograde pyelogram
4 The presence of cardiovascular disease
5 Albuminuria with hematuria

TABLE 2

1 Sudden renal pain with hematuria
2 Associated septic state, gastroenteritis, phlebitis, pneumonia, etc
3 Tender mass in renal area
4 Chills, fever and progressively downhill course
5 Pyelograms show distortion or incomplete filling

On the ninth hospital day sudden left upper quadrant pain developed at which time the patient's previously normal temperature rose to 101 2F The white blood count rose to 18,500 and blood culture was obtained This subsequently revealed no growth Catheterized urine was seen to contain 3+ albumin, 0–2 white blood cells and an occasional red blood cell per high power field The chest x ray was unchanged and physical examination was said to reveal a regular cardiac rhythm, blood pressure 108/90, but no other physical findings were recorded Excretory urograms revealed normal excretion of the dye on the right but at no time during the serial study was the left kidney visualized She was given 100 mg of Demerol at 4 hour intervals and 400,000 units of penicillin with 0 5 gm dihydrostreptomycin once daily Her pain slowly increased in intensity and migrated to the left renal area and nausea developed During the ensuing 2 days the pain persisted as did the nausea, however, the temperature slowly dropped to 99F At this time urologic consultation was requested Examination showed tenderness to light palpation of the left kidney area There were no other significant findings on physical examination A catheterized urine specimen revealed no change, Gram stain showed no bacteria The culture and sensitivity test ordered at that time subsequently revealed no growth. Blood urea was 37.7 mg. Cystoscopic study was advised.

Cystoscopy the following morning showed a normal bladder and clear bladder urine. Left ureteral catheterization was accomplished without meeting obstruction; a small amount of bloody urine was obtained. Indigo carmine appeared from the right ureteral orifice in 4 plus concentration in 5 minutes and 30 seconds. After a 16 minute wait no dye appeared from the left. Left retrograde pyelogram was entirely normal. Diagnosis of left renal thrombosis was made and nephrectomy was advised (fig. 1).

The following day the referring internist and the patient consented to surgical intervention. Further laboratory study showed the prothrombin time to be 18.4 seconds (40 per cent), carbon dioxide combining power to be 56 volumes per cent and venous coagulation time to be 21 minutes.

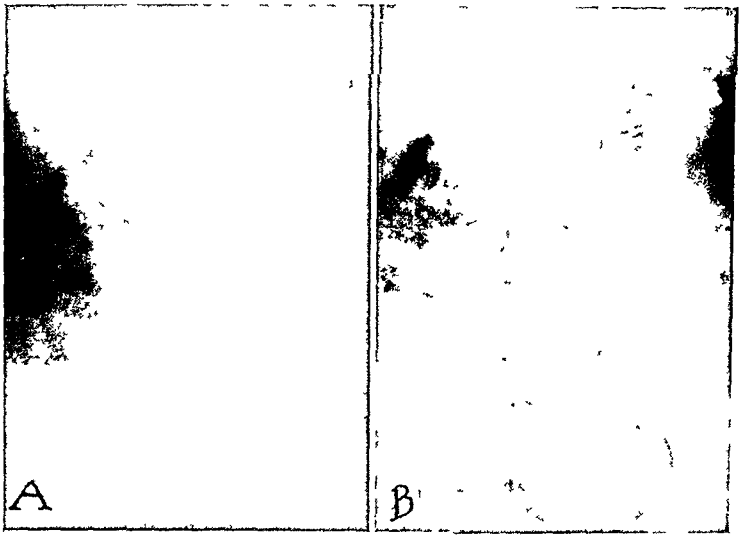

FIG. 1. *A*, excretory urogram showing functionless left kidney. *B*, normal left retrograde pyelogram.

At operation the perirenal fat was noted to be wet; the kidney was freely movable and the entire upper third was seen to be congested and dark red in color; the pelvis contained dark blood. No abnormality of the pedicle was palpable. Routine nephrectomy was done.

The pathologist's report (courtesy of Dr. Frank Tanner) revealed a distinct area of infarction and necrosis of the upper pole and he noted that grossly the specimen had the appearance of a kidney which had become infarcted secondary to thrombosis. The report of microscopic examination is quoted. "Sections taken through the kidney within the upper pole show a rather marked degree of infarction and early necrotic changes within the kidney parenchymal tissue. In this area there is complete loss of normal architecture with no well-defined tubules and glomeruli. In some areas the kidney parenchymal tissue is so indistinct as to be unrecognizable. There is also a chronic and acute inflammatory reaction associated. There is considerable deposition of brownish disintegrated blood pigment. There is also marked thickening and sclerosis of some of the vessels and this probably is upon a distinct arteriosclerotic basis Many of the larger arterioles show almost complete occlusion, due to the arteriosclerotic change" See figure 2

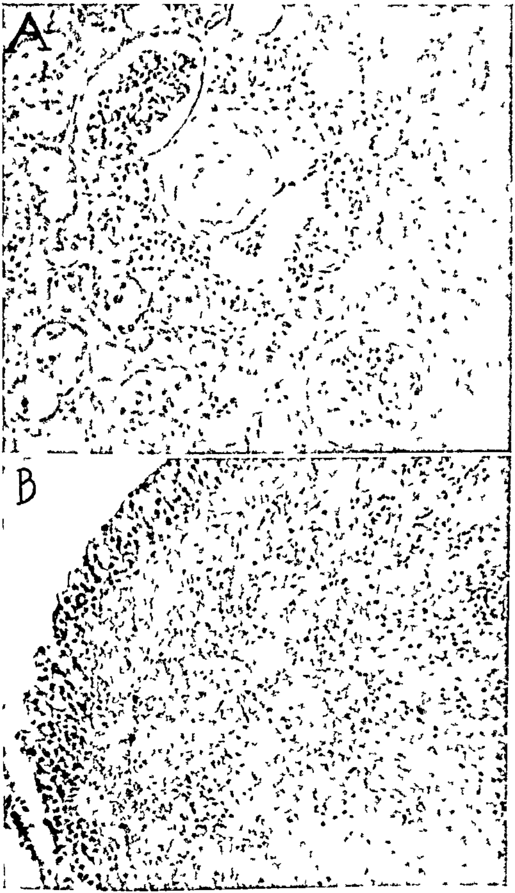

Fig 2 *A*, section shows relatively normal glomeruli and tubules Thickening of small arteries is demonstrated *B*, section taken at pelvis to demonstrate subepithelial hemorrhage adjacent to area of infarction This process accounts for hematuria occurring in these cases

On the first postoperative day the patient experienced transient substernal pain and was placed on quinidine and nasal oxygen Except for temporary moderate abdominal distention the remainder of the convalescence was normal She was carried along on quinidine, the penicillin-dihydrostreptomycin mixture and irregularly administered dicumarol as needed to maintain the prothrombin time below 40 per cent (18.4 seconds). The patient was discharged on the fifteenth postoperative day on three grains of quinidine at 6 hour intervals, free of complaints.

Follow-up examination in the office approximately 1 month later showed the patient to be in excellent condition with no further complaints referable either to the cardiovascular system or the urinary tract.

Case 2. This case is presented to demonstrate the recovery of function which occurs following arterial occlusion as demonstrated by urographic study and to re-emphasize the picture of arterial infarction resulting from mitral stenosis and fibrillation. Mrs. E. H., a 44 year old white housewife, was admitted to the Lincoln General Hospital by her internist on March 30, 1949, because of diffuse upper abdominal pain of colicky nature which began 2 days prior to admission. She had acute rheumatic fever in childhood with resulting mitral stenosis and she had experienced several episodes of decompensation. The significant physical findings were cardiac enlargement to the left with a diffuse apical pulsation, diffuse blowing systolic murmur transmitted to the left and frequent extrasystoles. The abdomen was tender to palpation in the left upper quadrant and considerable gas was evident upon percussion. The blood count showed 86.6 per cent hemoglobin, no red cell count, 15,600 white blood cells, the differential revealed 80 polymorphonuclear leukocytes and 20 lymphocytes.

A voided urine specimen was clear amber, pH 5, specific gravity 1.024, albumin 4 plus and microscopically 50 white blood cells and 3–4 red blood cells per high power field were noted. Following sedation and enema the patient was relieved of her distress and left the hospital.

She returned the following day complaining of severe left upper abdominal pain and loose stools. Examination revealed the maximum tenderness to be in the left flank and costovertebral angle area. She was decompensated. The white blood count was unchanged but the differential revealed a shift to the left. Urinalysis revealed a clear straw-colored specimen, pH 7.5, albumin 1 plus and 12–15 white blood cells and red blood cells per high power field on microscopic examination. The electrocardiogram revealed auricular fibrillation. She was sedated and digitalized. Her temperature rose to 101F. In spite of her decompensation and apparent serious status excretory urograms were obtained on May 4, 1949. These revealed incomplete filling of the upper calyx and pelvis on the left. Her precarious status was thought to preclude cystoscopic study and the the consulting urologist advised supportive measures and repetition of excretion urograms when her condition permitted. Catheterized urine was normal except for trace of albumin. After several days of cardiac therapy and concomitant penicillin and sulfadiazine administration the pain and fever subsided. On May 14, 1949, excretion urograms were entirely normal (fig. 3). She continued a febrile but slowly improving clinical course and was dismissed 2 weeks later after negative blood cultures and stool studies with a diagnosis of non-specific colitis and mitral stenosis with auricular fibrillation.

She was readmitted on June 18, 1952, because of severe pain in the left flank and abdomen of several hours' duration, with nausea and vomiting During the past three years she had been maintained on digitalis and had followed a course typical of a cardiac invalid Examination revealed the same cardiac findings The left renal area was markedly tender and muscle splinting was present Her temperature was 100F, admitting diagnosis was "left kidney lesion, question of possible tumor " A catheterized urine specimen was reported clear straw, pH 5,

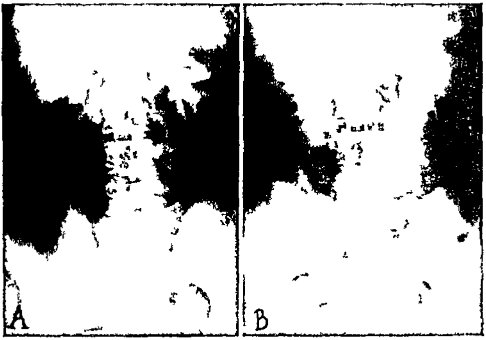

Fig 3 Excretory urograms taken 10 days apart revealing return to normal of left kidney

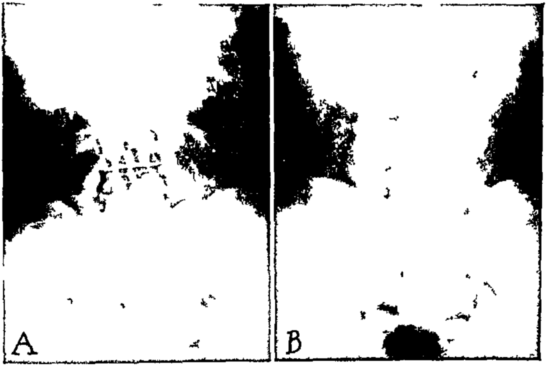

Fig 4 *A*, excretory urogram showing lack of left renal function *B*, normal left retro grade pyelogram

specific gravity 1 011, no sugar, acetone or diacetic acid Gram stain occasional red blood cells and white blood cells, no bacteria Culture produced a growth of Gram negative bacilli found to be sensitive to aureomycin, terramycin, and penicillin Blood count 79 per cent hemoglobin, 4,370,000 red blood cells, 18,250, white blood cells, differential revealed 82 polymorphonuclear leukocytes and 17 lymphocytes and 1 monocyte Blood urea was 85 6 mg Sedimentation rate was 25 5 mm for 60 minutes Excretory urograms showed a normal right kidney but no excretion of the dye on the left. Urologic consultation was obtained and a provisional diagnosis of left renal thrombosis was made. Cystoscopic study was advised and completed the following day. This examination revealed a normal bladder with clear bladder urine. Rhythmic efflux of clear urine from the right ureteral orifice was noted. The left orifice was seen to contract but there was no efflux of urine. The left ureter was easily catheterized, no urine was obtained. Retrograde pyelogram was made (fig. 4). A diagnosis of aseptic infarction was made. Two days later the blood urea had risen to 94.4 mg., and 2 days later to 116.6 mg. During this time nephrectomy was advised but refused because of the patient's cardiac status. She was given supportive care during this time and sedatives. Her pain progressively decreased in severity and her temperature was normal. Three days later the urea dropped to 61.1 mg., and on July 1, 1952, the thirteenth hospital day the urea was 34.8 mg. Further excretory urograms were refused. The volume of urine decreased to 1200 cc the day the urea was most elevated and progressively increased as the urea approached normal. A urea clearance test obtained on July 1, 1952 showed clearance of 18 cc per minute or 33 per cent of standard clearance. The sedimentation rate remained unchanged.

SUMMARY

Two cases of renal thrombosis have been presented. One was diagnosed preoperatively and treated by nephrectomy. This case demonstrated occlusion of smaller vessels of sufficient number, however, to produce infarction of one third of the kidney.

The second was an unproved diagnosis but presented a symptom complex typical of arterial infarction.

Subjective complaints directed to the kidney in a patient suffering from cardiovascular disease and cardiac arrythmias particularly should suggest the probability of renal thrombosis.

The question arises as to whether the first case might not have been embolic. Since sections of the opposite pole of the kidney failed to show any evidence of emboli it is believed that this was thrombosis rather than embolism.

The propriety of nephrectomy in this case is also questioned. At operation severe damage to the organ was apparent and thrombosis of larger vessels was suspected. Further there was an awareness that areas of infarction such as this result in hypertension, a particularly undesirable state in such a patient. Finally, since infection in this area was suspected the probability of septic infarction was considered.

It is regretted that facilities for arteriography were not available to augment the study of the cases.

1016 Sharp Bldg., Lincoln 8, Neb.

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GROSS HEMATURIA IN SICKLE CELL DISEASE

HERLUF G LUND, JUSTIN J CORDONNIER AND KENNETH A FORBES

From the Department of Urology, Veterans Administration Hospital, Jefferson Barracks, Mo and the Department of Surgery, Washington University School of Medicine, St Louis, Mo

Since the advent of urology, hematuria has been a major source of concern to the urologist, particularly in regard to essential or idiopathic hematuria Only recently has sickle cell disease been considered as one of the causes of idiopathic or essential hematuria Abel and Brown[1] in 1948 were the first to report on the incidence of gross hematuria occurring in a patient with sickle cell anemia This paper was soon followed by the report of a similar case by Fetter[2] In 1950 Goodwin, Alston, and Semans[3] were the first to suggest that sickle cell disease could be one of the underlying causes of essential hematuria in colored people They reported seven cases with gross hematuria, five with sicklemia, or sickle cell trait only Since then, eighteen other cases have been added to the literature,[4] [5] [6] [7] [8] a total of 27 cases in all The largest number of cases reported were those presented by Harrison and Harrison[9] at the American Urological Association meeting in June 1951 They presented 9 cases in six of which nephrectomy was performed

We have observed 7 cases of gross hematuria in colored patients proven to have sicklemia With one exception, the bleeding has been unilateral In that case there was a recurrence of gross hematuria from the remaining right kidney four years after left nephrectomy for uncontrollable bleeding

CASE REPORTS

Case 1 J T , a 43-year old colored man, was admitted to the hospital on September 6, 1951, complaining of gross painless hematuria of 10 days' duration The past history revealed that in May 1946, he had a three-day episode of hematuria which ended abruptly Hematuria again recurred in May 1947, with the only other symptom being that of a tired feeling across his lower back When admitted to the Veterans Administration Hospital, Jefferson Barracks, because of the persistent hematuria, complete blood chemistries were found to be within normal limits Red blood cell count was 5,000,000, hemoglobin, 13 7 gm The urine was grossly bloody throughout and no bacteria or increase in white blood

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Read at annual meeting, South Central Section, American Urological Association, Hot Springs, Ark , October 1, 1952

Presented with permission of the Chief Medical Director, Division of Medicine and Surgery of the Veterans Administration, who assumes no responsibility for the opinions expressed by the authors

[1] Abel, M S and Brown, C R J A M A , **136:** 624, 1948

[2] Fetter, F and Schnabel, T G Geriatrics, **4**. 309, 1949

[3] Goodwin, W E , Alston, E F and Semans, J H J Urol , **62:** 79, 1950

[4] Harwell, W , Patterson, R. H and Diggs, L W Ann Surg , **133:** 641, 1950

[5] Ryan, J E and Fuller, R N U S Armed Forces Med J , **2**· 623, 1951

[6] A report by personal communication to M Price Margolus, M D of a case of sickle cell disease complicated by hematuria seen at the Naval Hospital in Philadelphia (Med , **30:** 357, 1951)

[7] Henderson, A B Am J Med , **9:** 757, 1950

[8] Creecy, A A , Varano, N R and Hurdle, T G Virginia Med Monthly, **78:** 643, 1951

[9] Harrison, F G and Harrison, F G J Urol , **68**· 943, 1952

cells was noted. Urine cultures showed no bacteria. (Three cultures for tubercle bacilli were also negative.) Cystoscopic examination revealed bloody urine spurting from the left ureteral orifice, clear urine from the right. Excretory and retrograde pyelograms were normal. A nephrectomy was performed August 8, 1947, because of profuse, persistently uncontrollable bleeding.

Grossly, the kidney appeared normal except for a diffuse brownish tinge to the parenchyma. Microscopic examination failed to reveal any unusual histological findings. The postoperative course was uneventful; and the patient did well until September 6, 1951, when he was readmitted to the hospital for gross, painless hematuria of 10 days' duration. His only complaints were of a vague backache and a dull pain particularly of the left flank. The urine was grossly bloody, and revealed occasional white blood cells and rod-shaped bacteria. Complete blood studies were within normal limits. Red blood cell count was 5,100,000; hemoglobin, 14.9 gm. Sickle cell test was reported as negative. The excretory urogram was read as normal except for a compensatory enlargement of the right kidney. Eight days after admission the urine became clear. A repeat sickle cell test on October 19, 1951, and several others were positive. The microscopic sections of the kidney removed in August 1947, were then reviewed and sickling of the erythrocytes and congestion of the small vessels, capillaries, and glomeruli were noted (fig. 1). An alkali denaturation test of the patient's blood was made which was diagnostic of sickle cell trait.

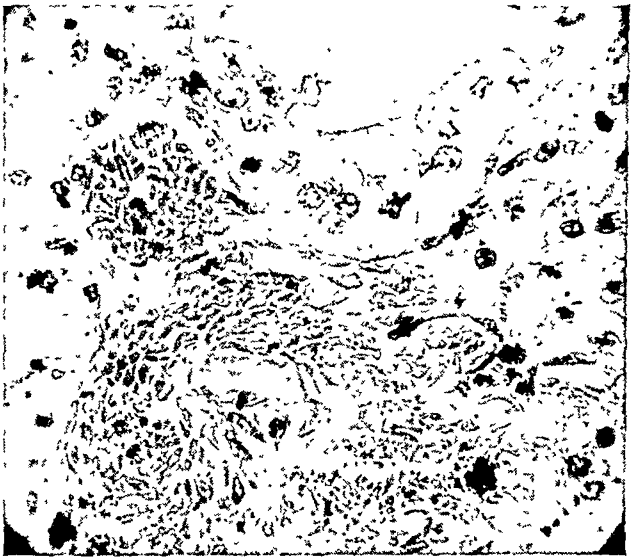

FIG. 1. Case 1. Photomicrograph of kidney showing congestion of vessel with sickled erythrocytes, hemorrhage and hemosiderosis. ×600.

Case 2. W. C., a 27-year old Negro, was admitted to the hospital on October 11, 1951, complaining of soreness and tiredness across his back and painless hematuria of 1 day's duration. Past history and physical examination were nonrevealing. Cystoscopy performed the day of admission revealed bloody urine spurting from the left ureteral orifice, clear urine from the right. Excretory and retrograde pyelography were in all appearances normal. Urinalysis showed no bacteria or pyuria Hematology and blood chemistry studies were all within normal limits except a white blood cell count of 4,450 and sickling of erythrocytes (fig 2) Urine cultures were negative Tubercle bacilli cultures were negative on three successive days Hematuria ceased two days after admission Alkali denaturation test was positive for sickle cell trait

Case 3 W W, on April 30, 1951, was admitted to the hospital because of painless gross hematuria of 2 weeks' duration There were no other symptoms A previous episode of hematuria in 1947 had been treated at Hines Veterans Administration Hospital with no apparent etiology or sequelae Physical examination revealed a normal 54-year old Negro, the only pertinent findings being bilateral arcus senilis and medial pterygiums Urine was grossly bloody and contained many white blood cells, with mixed coccal and bacillary infection Laboratory tests were reported as red blood cells 5,210,000, hemoglobin 15 2 gm, white blood cells, 8000 Cystoscopy revealed bloody urine to be spurting from the left ureteral orifice Urine culture showed scant growth of Proteus from the right kidney Excretory and bilateral retrograde pyelograms were normal Left perirenal air insufflation showed normal kidney outline Since hematuria persisted, a nephrectomy was done on May 4, 1951 Grossly, the surface of the kidney showed a few areas of splotchy redness up to 5 mm in size The mucosa of the pelvis presented a mottled dark red appearance with extension into one calyx, and with redness of the corresponding papilla Microscopically these dark red areas were found to be areas of fresh hemorrhage The parenchyma in the same areas was infiltrated by mononuclear cells and a few polymorphonuclear cells There was also marked congestion of the glomeruli Due to the fact that the pathologist could not explain the hemorrhage on the basis of the minimal pyelonephritis found, the patient was rehospitalized on November 27, 1951, for further studies The sickle cell test was positive, and the patient was proven to have sicklemia (sickle cell trait) The microscopic sections of the kidney were then reviewed and the erythrocytes

FIG 2 Case 2 Sickling of erythrocytes typical of those found in all patients in this series ×300

showed sickling within the engorged vessels and areas of hemorrhage in the parenchyma and pelvis (fig. 3).

Case 4. V. T., a 32-year old colored man, was admitted to the hospital on March 12, 1951, with a history of bilateral flank soreness for the preceding 3 years, and the passage of grossly bloody urine for 5 days. A brother of the patient had also noted intermittent gross hematuria for the past several years. Past history was noncontributory. The physical examination was negative except for a urethral stricture which was easily dilated. Laboratory findings were red blood cells 3,520,000, hemoglobin 11.5 gm., white blood cells 4,500, and sickle cell test positive. All other tests were within normal limits. Cystoscopic examination on March 19, 1951, revealed bloody urine coming from the left ureteral orifice. Excretory and retrograde pyelograms were read as normal. Urine culture from the left kidney was negative, as was the guinea pig inoculation for tubercle bacilli. Perirenal air insufflation on April 6, 1951, showed a normal kidney outline. Alkali denaturation test revealed the patient to have sickle cell trait.

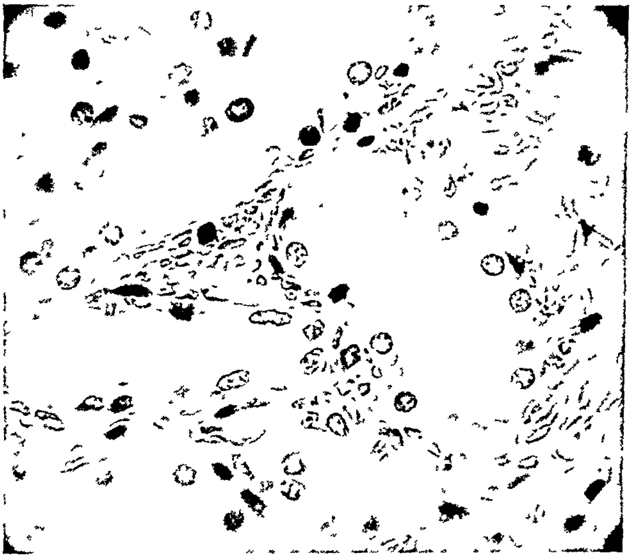

FIG. 3. Case 3. Photomicrograph of kidney showing congested vessels and hemorrhage into parenchyma. × 600.

Case 5. G. D., a 35-year old Negro, noted onset of painless gross hematuria with the passage of a few blood clots on February 2, 1952. He also noted an increase in frequency of urination with nocturia 2 or 3 times for 7 days prior to his admission on February 24, 1952. There were no other urological symptoms; no history of chills or fever. Temperature was normal. Upon admission, urinalysis revealed many white blood cells with mixed coccal and bacillary organisms. The patient was cystoscoped in spite of the presence of urinary infection and found to have hyperemia of the posterior urethra, inflammatory changes of the trigone and bloody urine spurting from the right ureteral orifice, clear urine from the left. Laboratory studies revealed sickling of the erythrocytes 100 per cent and the presence of sickle cell trait. All other tests were within normal limits. Excretory and retrograde pyelograms were read as normal Three days after the patient was placed on antibiotics, the urine became negative for bacteria but gross hematuria continued Urinalysis on February 28, 1952, microscopically showed many red cells, occasional white blood cells and no bacteria Bleeding ceased abruptly on February 29, 1952, and has not recurred

Case 6 W T, a 35-year old colored man, was admitted on February 29, 1952, complaining of painless hematuria and a tired aching feeling across the lumbar region of 5 days' duration Physical examination revealed no abnormalities Urinalysis Urine was grossly bloody without increase in white blood cells, or presence of bacteria Cystoscopic examination revealed bloody urine coming from the left ureteral orifice Retrograde pyelo-ureterogram of the left kidney, as well as the excretory urograms, were read as normal Laboratory studies were all within normal limits including three urine cultures for tubercle bacilli The sickle cell test was positive The patient was found by the alkali denaturation test to have a sickle cell trait Hematuria became intermittent on the second hospital day and remained so up to the day before discharge

Case 7 C B, a 31-year old colored male laboratory technician, complained only of painless hematuria of 4 days' duration before hospitalization on April 22, 1952 Urological history was otherwise negative Past history and physical examination were noncontributory Bloody urine was seen spurting from the left ureteral orifice on cystoscopy Excretory and left retrograde pyelograms were read as normal Urine cultures from the left kidney were negative, including those for tubercle bacilli Papanicolaou test was negative Laboratory tests revealed the patient to have sickle cell trait He continued to have hematuria up to June 18, 1952, and has had similar episodes intermittently ever since

DISCUSSION

Seven cases of gross hematuria occurring in patients with sickle cell trait are presented In two of these nephrectomy was performed because of uncontrolled bleeding These patients were studied carefully in respect to all known causes of hematuria and none were found There was only one in which the hematuria could questionably have been caused by an upper urinary tract infection, such as acute pyelonephritis If this were true, the patient did not present the usual signs and symptoms, such as chills, fever, and costovertebral or flank tenderness and pain All standard methods of controlling bleeding including repeated renal pelvic lavage were unsuccessful

Laboratory studies in these cases included tests for blood dyscrasia, cultures for tubercle bacilli, and in the last 4 cases Papanicolaou stains In all cases, sickle cell tests were made using the rapid method, sodium metabisulfite (sealing the slide with petrolatum) The per cent of sickling of the erythrocytes on repeated tests varied in one case as much as 0 per cent to 80 per cent No explanation is readily apparent for the wide variation of per cent of sickling of the erythrocytes at different intervals This variation was also noted by Neel,[10] who found similar results in a study of 310 cases of patients having sickle cell trait Abel and Brown[1] stated that they were unable to demonstrate sickling in the peripheral blood, but noted such in the microscopic sections of the kidney.

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[10] Neel, J V Blood, 6 389, 1951

Sickling is an inherent property of the red blood cell and not dependent on external factors other than a low oxygen tension. When sickling occurs, the cell instantly loses its easy flexibility and appears fixed and rigid. Dresbach[11] in 1904 was the first to report the finding of sickled or elliptically shaped erythrocytes in a male colored student, while Herrick[12] in 1910 was the first to describe the findings of sickle shaped cells in a patient suffering from severe anemia. Since then, various studies have been made estimating that from 7 per cent (Killingsworth and Wallace[13]) to 13 per cent (Beck and Hertz[14]) of the Negro race have sickle cell disease, and a ratio of 1:40 of sickle cell anemia to sickle cell trait. The presence of sickling is definitely of hereditary nature and has been considered so since Emmel[15] first described the occurrence of sickling in a father and son. Huck[16] believes that sickling of erythrocytes is due to a dominant gene which produces sickle cell anemia in some persons, while in others only the sickle cell trait, designated as sicklemia. The hypothesis that the presence of a gene when represented twice would produce a homozygous state causing sickle cell anemia, but when only represented once, a heterozygous state causing sickle cell trait (Neel[10]), is sound in theory but not true to fact, as not all individuals develop sickle cell trait in certain types of mating.

In the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, the discovery was made that the hemoglobin of persons having sickle cell anemia differs from normal hemoglobin and that found in persons with sickle cell trait (Pauling[17]). Later, Pauling demonstrated that this abnormal hemoglobin differed electrophoretically from normal hemoglobin, the former moving as a positive ion, the latter as a negative ion under certain conditions. Hemoglobin from individuals with sickle cell trait contained a variable mixture of both hemoglobins. Pauling also suggested that the presence of this abnormal hemoglobin when reduced might allow a different alignment of the molecules causing the sickling phenomenon. A simple technique was developed by Singer, Chernoff, and Singer,[18] whereby an alkali denaturation process destroyed the normal hemoglobin in one minute but not the hemoglobin in sickle cells. Using this method, patients with sickle cell anemia could be differentiated from those having sickle cell trait by use of a spectrophotometer. This specific test was done on all patients we have presented.

Pathologically, the kidneys removed in two of the cases presented were examined carefully by repeated sections; and in neither case could any reason be found to explain the hematuria other than the presence of sickled erythrocytes within the engorged small vessels, venules, capillaries, and glomeruli. These were also seen in the areas of hemorrhage (See figures 1 and 3.) After reviewing the literature, one is impressed by the fact that the presence of hematuria in this disease is probably more common than heretofore realized, and many of the past reported cases of unexplained hematuria in colored patients could possibly have been caused by this disease. In autopsies on patients with sickle cell anemia, Diggs and Ching[19] reported the most common findings in the kidneys to be congestion of small blood vessels, thrombosis, hemosiderosis, infarction necrosis, and replacement of the parenchyma by scar tissue. These were also present in the spleen and lung. However, Kimmelstiel[20] believes that in sickle cell disease capillary stasis is usually transitory in nature, and rarely are true capillary thrombi formed which lead to ischemic infarction and necrosis. It is logical that the bizarre shape of the sickled erythrocytes, along with their increased rigidity, makes it impossible for the cell to pass through small capillaries and vessels, thereby becoming lodged and interlocked leading to stasis, congestion, and thrombus formation. It is also quite possible that these thin walled vessels which are congested, lying in an area of low oxygen tension, are altered in function and permeability with resulting hemorrhage into the parenchyma, collecting tubules, papillae, and pelvis. However, if this were true, we would expect bleeding elsewhere in the body with purpuric manifestations, but purpura has not been reported in sickle cell disease. Therefore, other factors must be involved in order to cause hematuria in this disease.

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[12] Herrick, J. B.: Arch. Int. Med., **6**: 517, 1910.
[13] Killingsworth, W. P. and Wallace, S. A.: South. Med. J., **29**: 941, 1936.
[14] Beck, J. S. P. and Hertz, C. S.: Am. J. Clin. Path., **5**: 325, 1935.
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[18] Singer, K., Chernoff, A. I. and Singer, L.: Blood, **6**: 413, 1951.

In these cases we have presented and those already reported, we can find no acceptable explanation as to why bleeding occurs in this disease, nor why it usually presents itself as unilateral hematuria, particularly from the left kidney. Not until we can understand the pathogenesis of the disease will we be able to treat these patients adequately.

We are not in accord with the beliefs of Harrison and Harrison[9] who advocate nephrectomy in patients with sickle cell disease having unilateral gross hematuria for two reasons. First, as pointed out by Bauer,[21] patients with sickle cell disease, particularly if unrecognized, are poor surgical risks. Second, we wish to emphasize the findings presented in our first case where gross hematuria recurred in the remaining kidney four years following left nephrectomy for the same symptom complex. This could happen in other cases of sickle cell disease where a nephrectomy was performed because of gross hematuria. We, therefore, believe that nephrectomy should be done only when bleeding results in a steadily increasing secondary anemia which cannot be controlled by repeated blood transfusions, and where all other known methods to control bleeding have failed. In most of the cases, we have noted that hematuria would cease without complications or sequelae.

SUMMARY

Seven cases of gross hematuria in colored patients with sickle cell disease are presented.

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[19] Diggs, L. W. and Ching, R. F.: South. Med. J., 27: 839, 1934.
[20] Kimmelstiel, P.: Am. J. Med. Sc., 216: 11, 1948.
[21] Bauer, J.: Arch. Surg., 41: 1344, 1940.

Pathological findings in the kidney removed because of uncontrolled bleeding in 2 cases are discussed.

Hematuria in these patients can only be explained on the basis of the presence of sickle cell disease.

Hematuria in patients with sickle cell disease is more common than heretofore realized.

Nephrectomy should not be considered unless persistent gross hematuria results in a progressive secondary anemia. In our experience most of the cases of hematuria have ceased without complications or sequelae.

The authors wish to thank Amos Chernoff, M.D., Department of Medicine, Washington University, Saint Louis, Missouri for his assistance in running the alkali denaturation tests on these patients. We also wish to thank Franz Leidler, M.D., Chief, Laboratory Service, Veterans Administration Hospital, Jefferson Barracks, Missouri for his assistance in the biopsy studies and the preparation of the photomicrographs.

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HYDRONEPHROSIS OF PREGNANCY FOLLOWING URETEROSIGMOIDOSTOMY

BAXTER A SMITH, JR

The hormonal theory of the etiology of hydronephrosis of pregnancy is generally accepted Women have borne children after ureterosigmoidostomy, but I know of no reported pyelographic demonstration of hydronephrosis of pregnancy with previous ureterosigmoidostomy

Rubovits and Arnkoff[1] showed films made at 10 weeks of gestation and 3 months postpartum and these showed no change; an excretory urogram at 6 months was reported to show very little function but increased dilatation Hinman[2] showed a film at 7 months' gestation which showed no increase in hydronephrosis over the prepregnant urogram

Hofbauer[3] demonstrated hypertrophy of the lower ureter and of Waldeyer's sheath in the latter months of pregnancy This hypertrophy plus the weight of the gravid uterus were thought to be the etiologic factors in hydronephrosis of pregnancy until the middle thirties, when the hormonal theory was developed Browne and Venning[4] showed by hormonal assay that the placenta replaced the corpus luteum in hormonal function at about the third month of gestation Gonadotropin is excreted in high levels during the first trimester and thereafter the level drops rather precipitously to normal Estrin and progesterone, secreted by the placenta, then rise progressively until they fall abruptly at delivery Pregnancy may be carried to term after castration if the removal of ovarian function occurs after the third month of gestation

Traut, McLane, and Kuder[5] determined the extent of dilatation of the upper urinary tract paralleled the degree of atony Van Wagenen and Jenkens[6] showed the fetus was not necessary to the development of hydronephrosis by removing the fetus of Rhesus monkeys after the first third (two months) of the pregnancy The placenta carried on to term with the appearance of or the progression of hydronephrosis When the placenta was expelled at term, the hydronephrosis involuted normally The placentas averaged 10 gm in weight so that uterine bulk and pressure of the gravid uterus on the pelvic brim were insignificant

CASE REPORT

R B DeG was a white woman aged 17 in 1946 The patient had tuberculous pyonephrosis, right, with marked tuberculous cystitis, and slight dilatation of the left lower ureter Right nephrectomy was performed in June of 1946, bringing the ureteral stump to the skin

Retrograde pyelogram in September 1946 showed increase in the left hydro-

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[1] Rubovits F E and Arnkoff, M J Urol 62 52 1949
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[4] Browne J S L and Venning, E M Lancet 2 1507 1936
[5] Traut H F , McLane, C M and Kuder A Surg Gynec & Obst 64 51 1937
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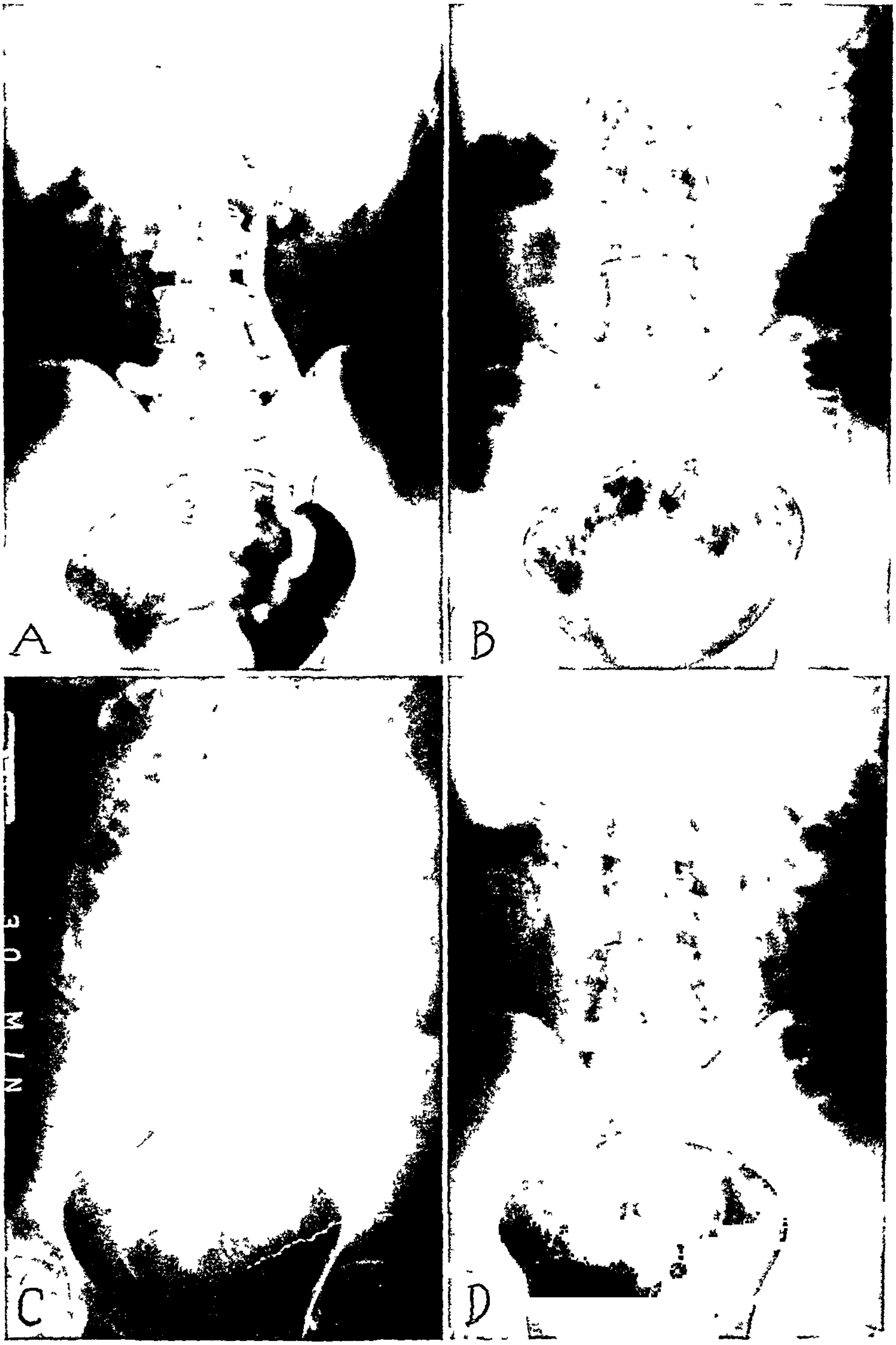

FIG. 1

ureter The right ureter had obliterated Four fulgurations of the tuberculous vesical involvement were performed and a 6 weeks' course of dihydrostrepto mycin (42 gm total) was given Neither had any appreciable effect An excretory urogram in June 1949 (fig 1, *A*) showed appreciable increase in hydronephrosis and hydro ureter Left renal specimens were again negative upon culture for acid fast bacilli Ureterosigmoidostomy was advised to preserve renal function This was done in August 1949

Marriage had occurred in June 1949 Pregnancy (unsanctioned medically) appeared and a decrease in the hydronephrosis and hydro ureter was shown in December 1949, at 3 month's gestation (fig 1, *B*) The enlarging uterus may be noted

Because of a previous tuberculous bartholinitis and the presence of the tuberculous bladder, albeit quiescent and now nonpalpable, Caesarian section was decided upon An excretory urogram made in June 1950, the day prior to section, showed a rather typical hydronephrosis of pregnancy with an "S" bend in the lumbar ureter (fig 1, *C*)

An excretory urogram made 3 months postpartum showed resolution of the upper urinary tract to normal (fig 1, *D*)

Pregnancy (again unsanctioned) recurred An excretory urogram was made 4 days after cesarian section in December 1951 Hydronephrosis was present of lesser degree than with the first pregnancy, the usual occurrence

Whitelow[7] et al, state that more than one half of their normal patients had completely involuted their hydronephrosis and hydro ureter at 4 days postpartum I believe one can see the site of anastomosis has risen out of the true pelvis in contrast to its position in the non gravid state (fig 1, *D*), negating the influence of pressure of the uterus on the pelvic brim

CONCLUSION

Clinical pyelographic support for the hormonal theory of the etiology of hydronephrosis of pregnancy is advanced in a case of pregnancy excluding the lower ureter, and probably uterine pressure on the pelvic brim, by ureterosigmoidostomy

305 Medical Arts Bldg , Minneapolis 2, Minn

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BENIGN TUBULAR ADENOMA WITH MALIGNANT TRANSFORMATION

WAYLAND K. HICKS

During the last few decades the malignant potential of renal adenoma has received increasing attention in the literature. Grawitz's theory of adrenal cells rests being the origin of hypernephromas has been more or less supplanted by the concept that renal adenocarcinomas arise from islets of nephrogenic tissue persisting in the renal cortex. It seems reasonable to assume that such islets of nephrogenic tissue could also be the origin of adenomas that might or might not change to adenocarcinomas. The large single adenoma has long been suspected as a source of renal neoplasm and many have noted the similarity in cell structure between adenoma and adenocarcinoma.

Small adenomas are a rather common finding, but large adenomas are infrequent. Kretschmer and Doehring reviewed the literature up to 1929, and found but seventeen of the latter. In 1942 Bugbee reported a large adenoma and stated these tumors were exceedingly rare. In 1944 Higgins added 6 cases to the literature, making a total of twenty-nine reported at that time. Of these large benign renal growths, the tubular adenoma is the rarest type.

In 1937 Creevy described a 3 cm. tubular benign adenoma which he believed was a potential malignant growth. In the *British Journal of Surgery* (October 1944) Buckley reported a large tubular adenoma of the kidney which was undergoing malignant changes. The case herewith reported is unusual in being a large (8 by 7 by 5 cm.) tubular adenoma undergoing malignant transformation.

CASE REPORT

H. S., a man, 50 years of age, was first seen in the office complaining of burning and smarting on urination. Three weeks previously he had retained his urine an uncomfortably long period of time, and the persistent burning and smarting followed. Several courses of urinary antiseptics previously given had failed to give relief. There were no other complaints.

On examination he was found to be a small, thin, wiry chap in excellent physical condition. He worked actively an eight hour day. Other than some palpable fullness in the left flank the physical examination was negative. There was no history of cancer in his family. The urine was loaded with pus cells. An initial excretory urogram indicated a normal right kidney but there was no visualized dye excreted from the left urinary tract. The left pelvis was then catheterized, and after 400 cc of hazy infected urine withdrawn, 350 cc of air was instilled, and a pyelogram demonstrated the presence of a hydronephrosis.

The patient was admitted to the hospital February 11, 1952. The laboratory studies showed a normal blood picture, except for 11,800 white blood cells. The urine was still filled with pus cells. The blood urea was 17.8 mg.

On February 13, 1952 the left kidney was removed without incident through

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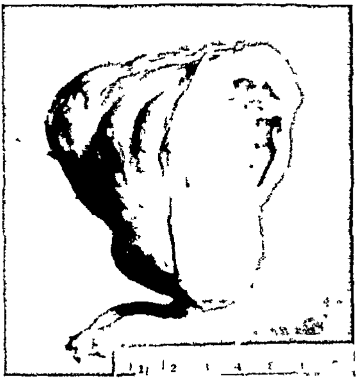

FIG 1

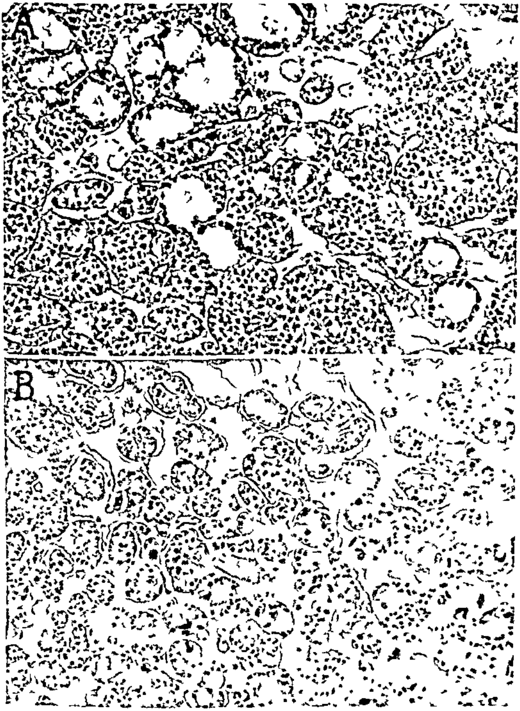

FIG 2

a curved lumbar incision. The cortex was thinned and the pelvis distended. The obstructive lesion was caused by the ureter being adherent anteriorly to a thick overhanging wedge of what appeared to be normal renal tissue. This adhesion had drawn the ureter sharply anterior and produced a kink at the ureteropelvic junction. My impression was that the adherence to the wedge of tissue caused the hydronephrosis, but there was no definite proof of this. If true, it would ascribe to the adenoma long standing benign properties, as the hydronephrosis was obviously of long development. Gross dissection following nephrectomy revealed the overhanging wedge of tissue to be a type of new growth only slightly and unevenly raised above the renal surface. Unfortunately, a camera failure spoiled a picture of the fresh postoperative specimen, but a view of the divided formaldehyde specimen was obtained (fig. 1).

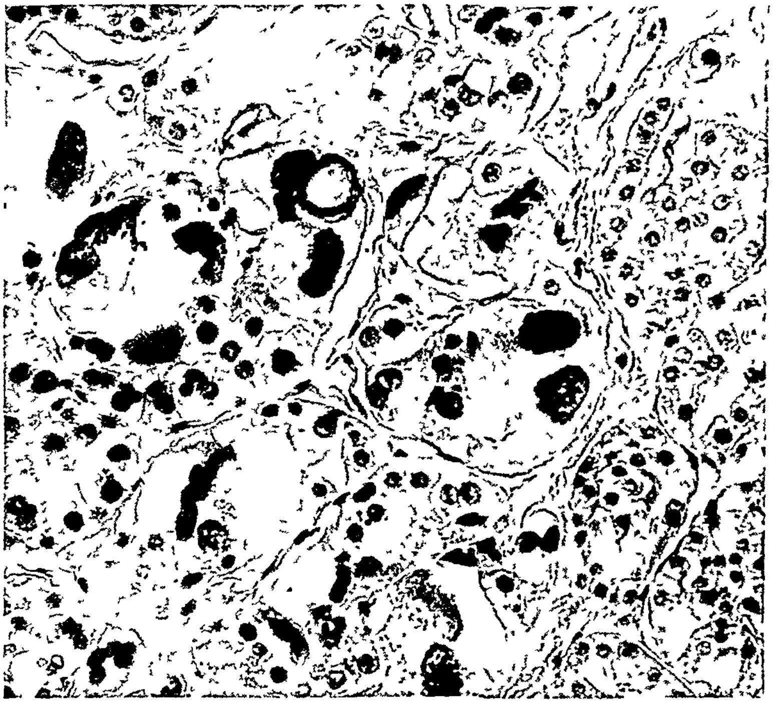
Fig 3

Histologically the tumor was composed of solid cords and cystic tubes of cells, varying considerably in size. Generally, the cords or tubes of cells were composed of individual cells showing rather sharp cellular boundaries. They were hypochromatic and resembled, to a certain extent, tubular epithelium.

There are certain areas in which the cells have taken on a malignant change. In these areas the cells are large and hypochromatic with numerous mitotic figures. These areas are definitely malignant. The individual structures are supported by a very loose connective tissue which contains numerous blood vessels. In some areas the connective tissue is more concentrated and sclerotic in appearance.

In this adenoma the first pathological sections appeared benign (fig. 2, *A*), but a later section (fig. 2, *B* and 3) fortunately showed an area of early malignant transformation Further studies throughout the tumor disclosed malignant changes in multiple sites Occasionally a single cell would be undergoing mitosis It was as if certain malignant potentials were gradually built up in these cells and then some unknown factor suddenly sparked them to activity simultaneously

DISCUSSION

Adenomas of the kidneys have been classified as papillary, alveolar, and tubular The majority are papillary in type, and are thought to be the result of a reparative process in sclerotic and degenerative kidneys Alveolar adenomas are described as resembling adrenal tissue and have columns of cords rather than glandular formation Tubular adenomas tend to reproduce renal tubules At times all three types can be found in the same tumor In 1946, Cristol, McDonald and Emmett found thirty seven small adenomas in twenty-two hypernephromatous kidneys, indicating, they thought, a higher incidence in kidneys containing carcinoma than in any non-malignant series examined at autopsy They believed that all adenomas, large or small, were potentially malignant Bell wrote that a distinction might be made between the multiple adenomas occurring in sclerotic kidneys and the single adenoma He thought that there was no clinical evidence that small multiple adenomas of sclerotic kidneys develop malignant cells Histogenesis suggests two theories of origin, first the reparative process in sclerotic kidneys and secondly an abnormality in embryologically imperfect tubules Herbert in 1952 points out that these lesions so often described as benign may in practice have cell structures and qualities making a benign or malignant diagnosis difficult It is beyond this author's scope to evaluate the literature on this pathological problem One can, however, surmise from the recent studies of adenomas that the adrenal origin of hypernephromatous kidneys is incorrect that adenocarcinomas of the kidney originate in adenomas, the type and percent still debatable, that while all renal adenoma are morphologically malignant, the large adenomas are more apt to develop clinical carcinoma

SUMMARY

A case is reported of a rare type of large tubular adenoma of the kidney The potential malignancy of this type of renal tumor is proved by a section showing an unusually early malignant transformation taking place The sudden simultaneous development of malignant cells in various parts of this previously benign growth is demonstrated A brief discussion of renal adenomas is given

505 Sixth Street, Sioux City, Iowa

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LEIOMYOSARCOMA IN A DOUBLE KIDNEY

DANIEL R. HIGBEE AND DALE M. ATKINS

By definition leiomyosarcoma is a malignant cellular tumor composed of anaplastic smooth muscle tissue. The most frequent site of occurrence is in the uterus and ovaries. The tumor is occasionally found in the gastro-intestinal tract, bladder, prostate, breast, retroperitoneal area, and kidneys.

Detailed statistics reveal the rarity of cases of leiomyomatous sarcoma of the kidney. In 1937 Mintz reported that 93 cases of all types of sarcoma of the kidney appeared in the literature. Relatively few cases have been added since that time. Of the total number of cases recorded, 18 have been leiomysarcoma. Berry, in 1929, reported the first case; the most recent one, Kretschmer's, was added in 1951, at which time he summarized 14 of the recorded cases. In addition, 2 cases have been reported by Petskovic and a case of bilateral leiomyosarcoma was reported by Bagolan. Cooke recorded the only instance in which extensive metastases have occurred. The case to be presented is the only one on record with extensive local recurrence.

Petskovic stated that myomatous tissue occurs in renal neoplasms in the following instances:

1) Subcapsular nodules or within the cortex (frequently found at autopsy).
2) Wilms's tumors.
3) Mixed tumors of connective tissue type (fibromyoma, fibromyolipoma).
4) Pure tumors of leiomyoma or leiomyosarcoma.

The etiological factors involved remain entirely speculative and range from theories concerned with congenital anlage (Cohnheim-Ribbert) to suggestions that these tumors result from inflammatory stimulation of smooth muscle tissue (Virchow).

A composite pathological picture of the recorded cases reveals that the tumors are subcapsular, encapsulated, and slow-growing until malignant change occurs at which time rupture of the capsule ensues and kidney destruction and local extension follow. In the course of development, softening, cystic degeneration, and hemorrhage into the cysts may occur (Busse, Counseller and Menville, Crabtree).

Microscopically, interlacing bundles of smooth muscle fibers containing blunt-ended, atypical nuclei are found. Mitotic figures are frequent as are bizarre giant multinucleated cells. As in other areas of the body, so in the kidney a leiomyoma may be difficult to distinguish from a fibroma necessitating in most instances the employment of special (Masson's or van Gieson's) stains.

Symptomatology is always attributable to the mechanical effects of the mass. Pain has been the presenting symptom in all of the reported cases. Hematuria, although present in the majority of kidney tumors, has been reported in only 4

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cases. X-ray, in addition to changes associated with tumor, may show calcified areas within the kidney shadow due to myomatous tissue of impaired vitality (Petskovic's case 1 and Crabtree's case).

Jacobs and Hoffman suggest that a radical nephrectomy be performed in cases of sarcoma of the kidney and recommend deep x-ray therapy at the site of the nephrectomized area.

A conclusive foundation, on which prognosis can be based, is not presented in the literature for in no instance is adequate follow-up data available. As stated by Golden and Stout, prognosis is as much dependent upon the anatomical site of the tumor as upon its histological character.

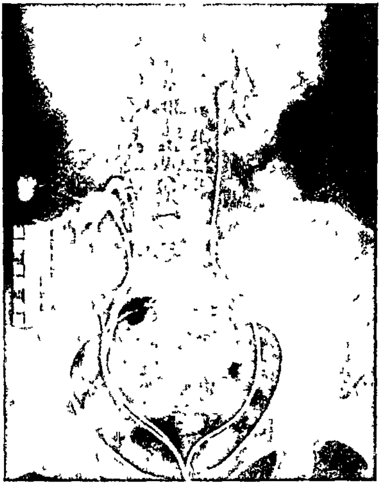

FIG. 1. Retrograde pyelogram showing double right kidney with tumor involvement

CASE REPORT

A 68 year old white woman entered the hospital October 26, 1950, with a history of right flank pain of 6 weeks' duration. There had been an 11 pound weight loss. Physical examination revealed a palpable, fixed, right upper quadrant mass. There was associated tenderness in the right costovertebral angle. Urinalysis was normal. Retrograde pyelography revealed a double right kidney with tumor involvement (fig. 1). Three days after admission a right nephrectomy was done and a large mass found involving the upper pole of the kidney.

The following is a pathological description of the lesion: "The specimen is a kidney with a superimposed mass at the upper pole. A ureter originates from both the tissue which is recognized as kidney and one surface of the whitish, moderately nodular, firm, and gristlelike superior mass. The mass referred to is apparently a neoplasm and the neoplasm is apparently separated from the underlying kidney by a fibrous capsule which is intact. It is completely surrounded by a separate capsule which shows no gross evidence of incompleteness. The neoplastic mass has greatest measurements of 8 and 6 centimeters. The kidney below is somewhat compressed by the overlying tumor mass and attains greatest dimensions of 6 and 3 centimeters (fig. 2).

"Microscopically the sections present a neoplastic structure which is separate from the kidney, sections of which are also presented and which is surrounded by a fibrous capsule which it does not invade. The tumor mass is composed of intertwining bands of smooth muscle fiber. In some regions these are tightly packed but show no other alteration of structure. Such areas blend with regions in which there are numerous mitoses and with areas in which the fibers are fragmented and numerous bizarre multinucleated cells are seen. Mononuclear leukocytes are sprinkled throughout such areas, and they are also more vascular than the densely packed, more differentiated regions. The sections of the kidney show no involvement by the tumor (fig. 3). Diagnosis: Leiomyosarcoma in a double kidney."

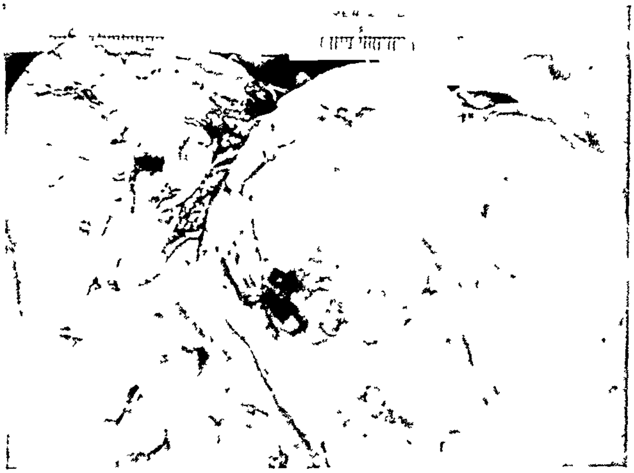

FIG. 2. Gross specimen showing an encapsulated neoplasm, right, compressing the adjacent kidney, left.

Convalescence was uneventful. A follow-up examination 5 months later revealed no evidence of recurrences. However, approximately 10 months after her first admission, the patient was readmitted to the hospital for the second time, with a complaint of pain in the right upper quadrant with radiation down the right thigh of 1 month's duration. Appetite was poor and there had been a 5 pound weight loss. Examination revealed a firm, fixed mass in the right upper quadrant. A laparotomy 2 days after admission revealed a large retroperitoneal tumor which involved the cecum and adjacent small intestine. A biopsy was taken and a recurrent retroperitoneal leiomyosarcoma verified.

Daily x-ray therapy was given to the abdomen for 11 days and the patient was ambulatory when discharged. A chest film one month prior to death revealed no metastases. At no time after discharge were there symptoms of intestinal

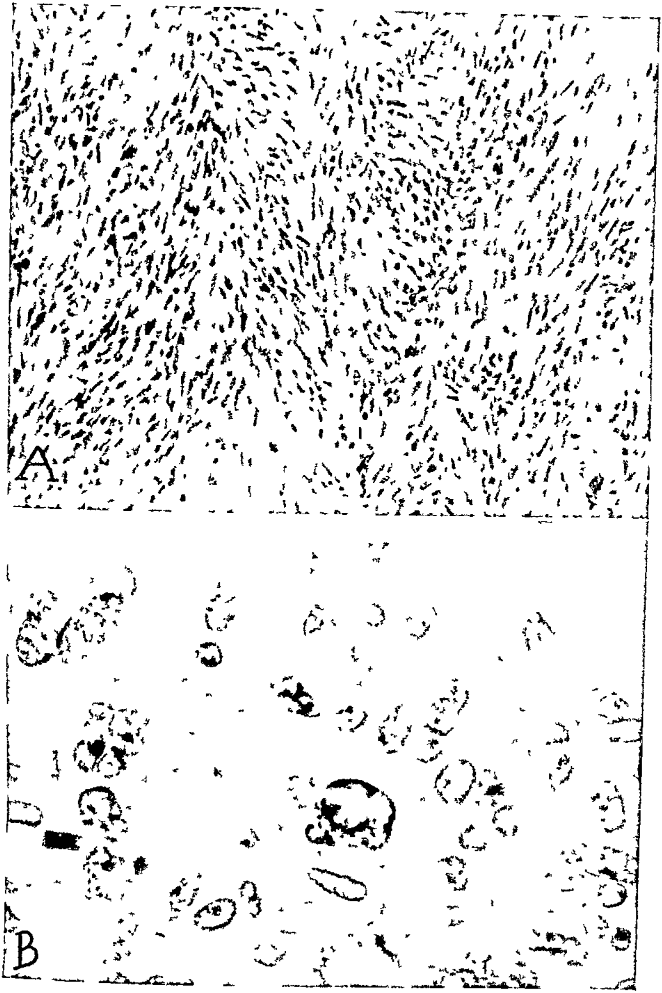

FIG 3 *A*, showing intertwining bands of smooth muscle fibers *B*, high power, showing blunt ended nuclei and bizarre giant multinucleated cells H and E stain

obstruction She expired November 12, 1951, approximately one year after the original nephrectomy No autopsy was obtained

SUMMARY

A case of leiomyosarcoma in a double kidney is presented and a brief review of the literature is given.

1117 Republic Bldg., Denver, Colo.

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NEPHRO URETERECTOMY AND HEMINEPHRO-URETERECTOMY IN INFANCY AND CHILDHOOD

HARRY M SPENCE

From the Urological Departments of the Dallas Medical and Surgical Clinic, Southwestern Medical School and the Children's Hospital of Texas, Dallas, Texas

The purpose of this paper is to discuss the indications for and the technique of nephro ureterectomy and heminephro ureterectomy in infancy and childhood as illustrated in a series of personal cases It is our opinion that the operation has not received the recognition and acceptance it merits and it is hoped that a presentation of our experiences may lead to a wider use of this procedure in suitable cases

Kelly[1] is credited with first carrying out a planned one stage nephro ureterectomy in 1898 Employing two relatively short incisions he followed the usual lumbar nephrectomy with a ureterectomy through an "inguinal" incision The indication for these early nephro-ureterectomies by Kelly was tuberculosis of the kidney and ureter

In 1921 Beer[2] introduced and popularized his "aseptic nephro ureterectomy" The essential features of this were 1) lumbar nephrectomy leaving the kidney attached to the ureter, 2) complete mobilization of the ureter through a pararectus incision and its severance at its junction with the bladder, and 3) withdrawal of the kidney and entire ureter in one piece through the original loin wound He gave as his indications for the operation 1) papillary tumor of the kidney pelvis or ureter, 2) tuberculosis of the kidney and ureter, and 3) a destroyed kidney with hydro ureter secondary to lower ureteral obstruction due to stone, stricture, or incompetent ureterovesical valve

In 1933[3] Beer recorded his further experiences with the operation He reported 40 cases of one stage nephro ureterectomy without a death, thus demonstrating that the added risk of removing the ureter through an accompanying pararectus incision was negligible Most of these 40 cases were done for tuberculosis or tumor Twelve of the operations were for extrinsic or intrinsic ureterovesical obstruction No mention was made of ureterocele as the cause of the obstruction, nor did he state that he had carried out the operation in infancy or childhood

Beer pointed out that the removal of the ureter through a second incision was much less formidable than extending the original kidney incision down to the external ring, which would be necessary to secure adequate exposure were the operation performed through a single incision He stressed that nephro ureterectomy permitted the removal in one stage of the entire disease process when advanced destruction of the kidney parenchyma was associated with ureteral stagnation He concluded that an initial extirpation of both kidney and ureter is much less difficult for both patient and surgeon than secondary ureterectomy for empyema of the remaining ureteral stump

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Read at annual meeting, South Central Section American Urological Association, Hot Springs Ark October 1, 1952

[1] Hunner, G L J Urol , 40 752, 1938 (Historical foot note, p 757)

[2] Beer, Edwin J A M A , 77 1176, 1921

[3] Beer, Edwin J Urol , 29 135, 1933

In answer to those who advocated performing the ureterectomy first through a lower abdominal incision before the nephrectomy, Beer pointed out that it is wiser to do the more essential part of any operation first, the essential part here consisting, of course, in the removal of the kidney itself. In case the patient's condition then did not permit further surgery, one might exteriorize the ureter for later ureterectomy. Furthermore initial section of the ureter commits one to nephrectomy, whereas in an occasional case exposure of the kidney might change the planned procedure in spite of the most careful preoperative work-up.

In the last two decades primary removal of the kidney and ureter through two incisions of varying types with the kidney or the lower ureter being attacked first has become firmly established as a standard procedure. The operation has been done with increasing frequency and as a result prolonged debilitating sepsis from failure to remove an infected ureteral stump has become less and less common. Nevertheless, cases of empyema of the stump and recurrent urinary tract infection due to poor ureteral drainage still occur as shown by the recent report of Stepita.[4]

INDICATIONS FOR NEPHRO-URETERECTOMY IN INFANCY AND CHILDHOOD

The indications for this operation in pediatric urology are, in general terms, found in and restricted to those cases where removal of an irreparably damaged kidney alone would leave behind a large nondraining or poorly draining ureteral pouch due to an impaired outlet of the ureter into the bladder. Here we believe primary removal of the ureter with the kidney is definitely advisable. Ureterovesical stricture, stenosis, and ureterocele have been the predominant causes of obstruction in these children in our series. Although attempts have been made to establish hard and fast rules as to when the ureter should be so removed, we believe each prospective case must be individualized. Delayed exposures on the excretory urogram up to two or three hours after injection as well as delayed films following retrograde filling of the ureter with contrast media have been the most helpful measures in reaching a decision. While the adequacy of drainage to be expected from the dilated ureter after nephrectomy may be estimated fairly well by reviewing such films, one should in addition take into consideration the clinical condition of the patient. In a child whose general health has been impaired by long-standing urinary tract infection, the immediate postoperative convalescence as well as the permanent recovery of health may well be enhanced by primary removal of the entire septic focus. In addition to the technical difficulties of a secondary ureterectomy, one must recognize that a child embarrassed by weeks or months of persistent urinary tract sepsis from an inadequately draining stump may be no better as a surgical risk than he was prior to nephrectomy alone. This viewpoint has been summarized well by Fagerstrom who states, "When properly employed with proper selection of cases, total primary ureterectomy will often circumvent many of the pitfalls of misguided conservatism."[5]

Although we realize that all urologists can present examples of markedly dilated ureters left behind after nephrectomy which subsequently regressed satisfactorily, one must also acknowledge that perhaps an equal number of cases have occurred in which there was little doubt in the operator's mind at the time of nephrectomy that the ureter would so regress, and it was left behind only to require a subsequent difficult ureterectomy Since in our own experience these two groups have more or less balanced themselves, it is now our policy, whenever we are uncertain as to the probable fate of the ureter, to resolve the quandary by removing it at the time of the nephrectomy One of the reasons for this attitude is that removal of the ureter, by the technique to be described below, is so simple that we feel that it does not appreciably increase the operative hazard even in an initially poor risk In other words, if the child can stand a nephrectomy, he can also stand the simultaneous ureterectomy Smooth convalescence and prompt return to health are the dividends

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[4] Stepita, C. T. and Newman, H. R.: J. Urol., **63:** 500, 1950.

[5] Fagerstrom, D. P.: J. Urol., **41:** 137, 1939.

CONTRA INDICATIONS TO NEPHRO-URETERECTOMY

Having liberalized the indications for the operation, we must review the contra indications which actually are the same as those to nephrectomy itself Congenital or surgical absence of the opposite kidney is, of course, an absolute contra indication to the operation The fact that examples can be cited of a solitary kidney sustaining life for months or years, which in the presence of a normal mate would unquestionably have been removed, emphasizes the point that one should not carry out nephro ureterectomy unless and until he is convinced by trial or past experience that any form of conservative operations or instrumentation to relieve obstruction and promote drainage would be nothing more than a futile gesture

Likewise where the disease process is bilateral with bilateral hydro ureters and hydronephrosis due to intravesical or bilateral ureterovesical obstruction, nephro ureterectomy would seem to be ill advised Here one cannot even aim at the ideal, but simply must salvage what is left of renal function In an occasional case, however, even though the "good" side is abnormal and shows obstructive changes, if the cause can be corrected, removal of a functionless septic pouch on the opposite side may take some of the burden off of the remaining parenchyma

A third contra indication to nephro ureterectomy is found in the case in which the obstructive lesion in the ureter is possibly remediable and the child is in reasonably good condition Here prolonged efforts at correcting the obstruction should have been tried and found wanting before recommending anything more radical

To return to our concern of the moment, however, which is the question of removing the diseased ureter as well as the kidney when one unequivocally has made up his mind that the latter should come out, we feel that the opinion of others as well as our own experience dictates concommitant ureterectomy

OPERATIVE TECHNIQUE

In this series and in our adult cases, we have had some experience with all the commonly used techniques and surgical approaches for nephro ureterectomy As our experience has grown, we have come to regard the principles of the Beer operation as the most sound. As carried out by us, the operation consists of the following steps:

Step 1. The kidney is exposed through a generous loin incision, the pedicle clamped, cut and ligated and the ureter freed down as far as possible by blunt dissection.

Step 2. The kidney is wrapped in a sterile towel and allowed to dangle by its attached ureter from the anterior angle of the loin incision, which is closed in layers with a drain at the posterior angle. This closure is snug but not tight where the ureter emerges at the lower end of the incision so as to permit its subsequent withdrawal.

Step 3. The child is now turned on his back and through a midline suprapubic extraperitoneal incision the ureter is picked up under vision where it crosses the iliac vessels. Traction by an assistant on the previously exteriorized kidney to render the ureter taut in the depths of the wound markedly expedites its identification and immediately differentiates the distended ureter from the bowel which it so often resembles in these cases.

Step 4. After the ureter has been found, it is stripped down to its entrance into the bladder (which should have been previously emptied) where it is sectioned and ligated and the kidney and entire ureter pulled out in one piece from above without spilling of contents. The operation is completed by closure of the lower wound with drainage.

While there are other satisfactory techniques, that just described is our current preference. Where the ureter and kidney seem too bulky to leave hanging out of the wound, a heavy ligature may be tied about the ureter, the ureter cut, and its upper segment and the attached kidney removed, leaving the ligature long to emerge from the loin wound for traction to later identify the lower ureteral segment through the midline incision.

We have found that the midline suprapubic approach to the lower ureter is preferable to any other in that it is bloodless, rapid, and anatomical. It gives unexcelled exposure of the ureter both where it crosses the iliac vessels and where it enters the bladder.

HEMINEPHRO-URETERECTOMY

In heminephro-ureterectomy, the pediatric urologist has the satisfaction of being both radical and conservative at the same time. Complete removal of a functionless half of a double kidney with its attached sausagelike ureter, combined with preservation of a substantial amount of normal parenchyma draining into the bladder by a normal ureter, fulfills both requirements.

The ease and safety with which a heminephrectomy for a double kidney may be carried out depends primarily on complete mobilization with meticulous dissection of the blood supply before making the incision into the kidney substance. The proper site for this incision is usually obvious in the type of case we are discussing here and is represented by the junction of the softened, thinned parenchyma with the normal feeling kidney substance.

If the anatomical pattern permits, it is desirable to secure the blood supply to the diseased segment extrarenally, but heminephrectomy is still feasible where the renal vessels branch only after entering the double kidney Here the maneuver is to compress the vascular pedicle between the index and middle fingers of the left hand and while steadying the kidney between the thumb and the remaining fingers, a shallow wedge is made at the site of election and the diseased segment removed Without releasing the vascular compression, horizontal mattress sutures of atraumatic "0" chromic catgut underpinned by Oxycel or fat are placed, snugly tied, and the pedicle released Any further bleeding is then controlled by additional mattress sutures A continuous over and-over suture through the capsule completes the closure and the remaining portion of the kidney is suspended in normal position

We have tried and abandoned as either unnecessary or ineffective other proposed techniques for heminephrectomy such as placing mattress sutures prior to the resection, the use of the electrosurgical knife, attempts to clamp and ligate individual vessels in the cut surface of the parenchyma and the more complicated suturing techniques such as the cobbler's stitch or the use of ribbon gut

CASE REPORTS

Case 1 DM&SC No 25311 BP A young adult man was seen by us 1 week after he had undergone an appendectomy, at which time the surgeon had felt a "large smooth mass lying at the brim of the pelvis in the midline, having the shape and consistency of a kidney" Questioning of the patient revealed that since early childhood he had suffered from backache, lower abdominal pain, and on frequent occasions had been treated for pus in the urine Excretory urograms showed no excretion of the dye on either side, although the bladder filled rapidly with the medium Cystoscopy showed marked cystitis with jets of clear urine from the left ureteral orifice and a "worm of pus" from the right one Indigo carmine appeared in normal time and concentration on the left, but none on the right Retrograde pyelograms showed a tremendous dilation of the entire right side of the urinary tract all the way down to the ureterovesical junction The left kidney lay entirely within the pelvis, but was otherwise normal (fig 1) On March 15, 1941, nephro ureterectomy was carried out with removal of the kidney through a loin incision and the lower ureter through a Gibson incision Following the operation, the patient's urine immediately became normal and has remained so over the years Whereas he formerly had been a frail, puny individual, he soon gained weight and strength and developed a robust physique

Case 2 T C H No MN612 JM A chronically ill 1 year old male infant had suffered from dysuria, pyuria and febrile bouts since the age of 2 months Urological studies showed a normal left kidney and right pyonephrosis with hydroureter due to obstruction at the ureterovesical junction (fig 2, *A*) There was no ureterocele and no reflux A No 5 ureteral catheter was passed with ease Because of the patient's general condition and the fact that he had a normal kidney on the left (fig 2, *B*), a right nephro ureterectomy was done through an oblique loin incision and a midline suprapubic incision (fig 2, *C*) The urine immediately cleared and the child has done exceedingly well since

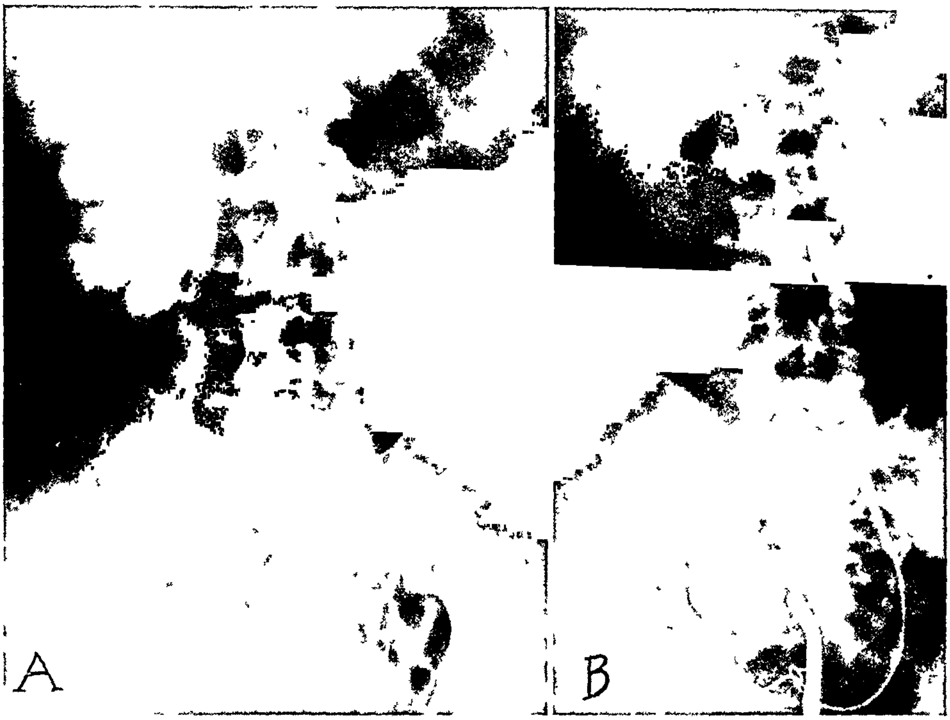

FIG. 1 Case 1. Bilateral retrograde pyelograms. Note that "normal" left kidney lies within the bony pelvis.

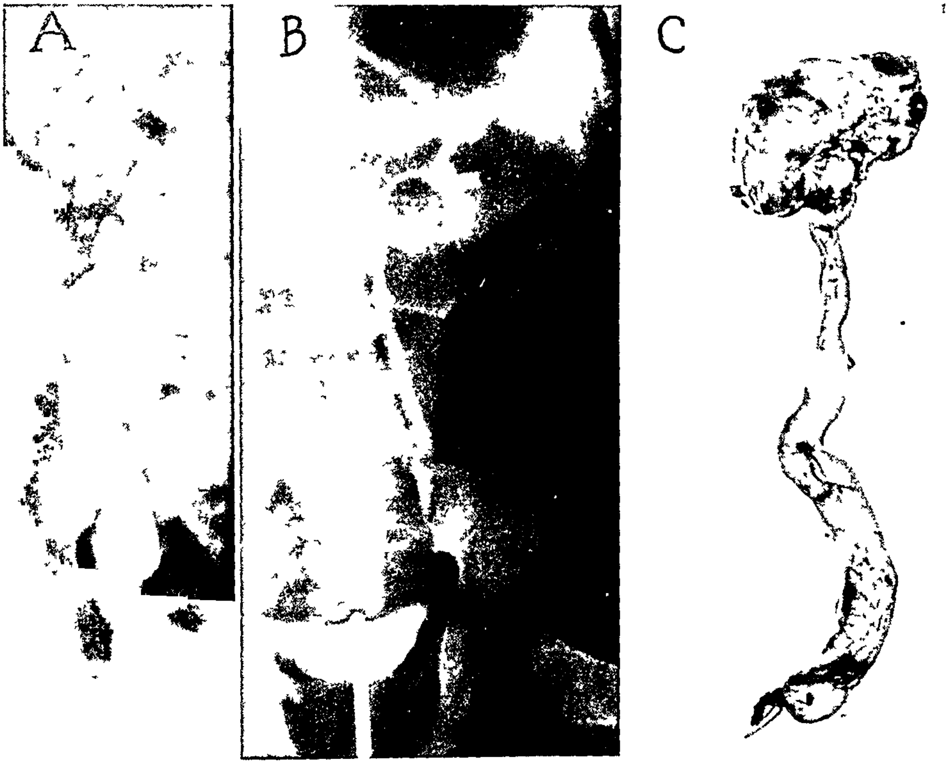

FIG. 2. Case 2. *A*, retrograde pyelo-ureterogram showing large hydro-ureter on right. *B*, normal left kidney. *C*, surgical specimen (compare with *A*).

Case 3. DM&SC No. A-7574 JBC. A male infant was seen at 5 months of age with the history of having been born with an imperforate anus for which a colostomy had been performed on the first day of life. He had experienced numerous febrile episodes with difficult urination and constant pyuria which failed to respond to medication. Complete cystoscopy under ether anesthesia showed a filiform contracture of the bladder neck which required dilation before the infant cystoscope could be passed. The bladder showed marked cystitis with a normal right ureteral orifice. The left orifice could not be found. Excretory urograms with delayed films showed a normal right kidney and a marked left hydronephrosis and hydro-ureter apparently due to an obstruction at the left ureterovesical junction (fig. 3, *A*). At the age of 6 months, a left nephro-ureterectomy was carried out through a single, long, oblique loin incision. The ureter was tremendously dilated and the kidney destroyed from obstruction and infection. Following the nephro-ureterectomy, the patient did remarkably well and gained weight and strength for the first time in his life. At the age of 3 years, an abdominoperineal operation with anoplasty and closure of the colostomy was done. The child is now 4 years old and in excellent health. Urograms show a normal right kidney and bladder and the urine is normal.

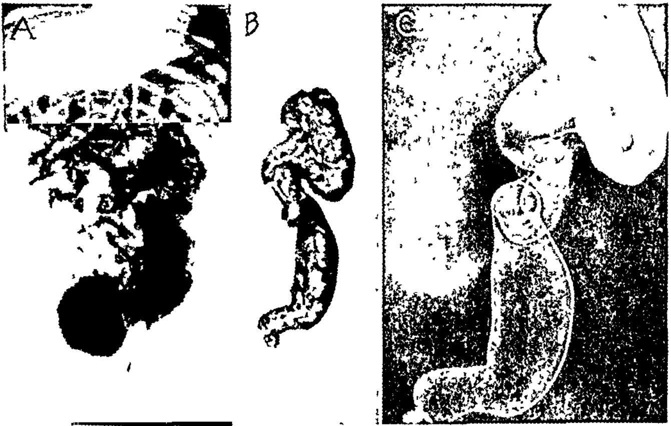

Fig. 3. Case 3. *A*, two-hour delayed excretory urogram showing large left hydronephrosis and hydro-ureter. *B*, surgical specimen removed by nephro-ureterectomy *C*, same injected with air. Note tortuosity of ureter.

Case 4. DM&SC No. L-3608 OHMjr. A 6 year old boy's complaint was "burning urination off and on for one year." Symptoms would clear temporarily with sulfonamides. There had been no fever, pain, nor other symptoms. Physical examination was normal except for a general appearance of chronic illness. The excretory urogram showed the right kidney to be smaller than average and the left kidney unusually large with distorted upper calyces. Since the excretory urogram was not diagnostic, cystoscopy was carried out with a precystoscopic diagnosis of hypoplasia of the right kidney and possibly a tumor or anatomical the panendoscope and a large amount of cloudy urine gushed out. Although a catheter could not be passed up the opening in the ureterocele, a clinical diagnosis of reduplication of the left kidney with probable hydronephrosis of the lower half was made and confirmed at operation where a tremendous hydronephrosis of the upper portion of the kidney was found with a tortuous dilated ureter extending downward. The lower portion of the kidney appeared normal and its ureter was of normal size. Heminephro-ureterectomy was performed through an extended loin incision (fig. 6, *C*). The patient did well postoperatively except for considerable dysuria which was attributed to the persistence of the collapsed ureterocele wall. Two months after operation the urine was normal and the patient was asymptomatic. Recent excretory urograms showed excellent function and drainage of the lower half of the left kidney.

Case 6. DM&SC No. C 6019 PKS. A 3 month old female infant had had no urinary tract symptoms until 6 weeks of age, at which time she began to cry with apparent colic and had high fever, which was thought to be a virus infection. She was treated with antibiotics with prompt response, but within a week symptoms recurred and pus was then found in the urine. It was noted that the child would start to urinate normally and then dribble a bit and cry throughout voiding.

Complete urological study showed the right side of the urinary tract to be normal, but on the left, the kidney appeared displaced downward and laterally. A massive ureterocele accounted for the symptoms of bladder neck obstruction. Putting these findings together, a diagnosis of a double left kidney with the ureter from the upper segment ending in the ureterocele was made and confirmed at operation. Since, in our experience, sizable ureteroceles in the small infant are best handled through the open bladder so that the mass of redundant tissue can be excised with immediate complete relief of the obstruction of the bladder outlet, this ureterocele was so removed through a suprapubic cystostomy. With the bladder opened, a large soft rubber catheter was passed through the opened ureterocele and a No. 4 ureteral catheter passed through the adjacent normal orifice on this side and pyelograms made (fig. 7, *A*, *B* and *C*). These showed a massively dilated tortuous ureter to the upper half of the kidney and a normal lower half.

The child did well postoperatively and voiding became normal. It is obvious from the urograms, however, that heminephro-ureterectomy will be necessary and this is further borne out by the fact that the child continues to have a large amount of pus in the urine.

Case 7. DM&SC No. 6819 PB. A 9 month old female infant had had repeated episodes of "cystitis and pyelitis" with gross pyuria since the age of 4½ months. She had received all the antibiotics and sulfonamide preparations with no sustained results. At 8 months of age, one month prior to being seen by us, she was cystoscoped by a very competent urologist who saw "a cystic yet pliable mass in the bladder." Following this cystoscopy, the child had an attack of straining and a mass protruded from the "vaginal opening." She was re-cystoscoped and the observer reported that the original mass had disappeared and normal ureteral orifices were present on each side with the opening of a "diverticulum" between the interureteric ridge and the vesical neck The child continued to have to strain to void and off and on a mass would protrude apparently through the vagina

We carried out complete urological investigation, including cystograms, excretory urograms, cystoscopy, and attempted ureteral catheterization with retro-

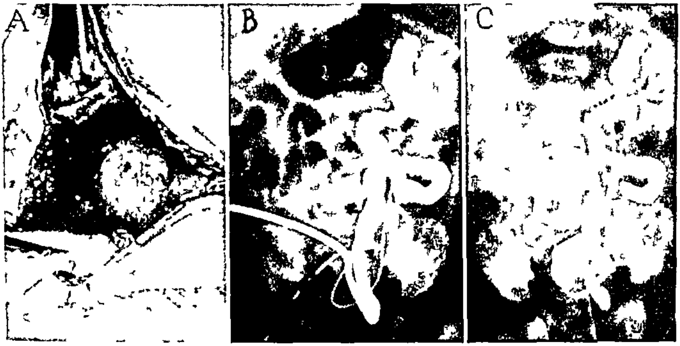

FIG 7 Case 6 *A*, ureterocele as seen through open bladder at operation *B*, after excision of ureterocele, large ureteral catheter has been passed through resulting large orifice and dye injected demonstrating dilated tortuous ureter to upper half of double kidney *C*, ureteral catheter which enters normal left orifice has been injected revealing a normal lower segment of ureter and of pelvis

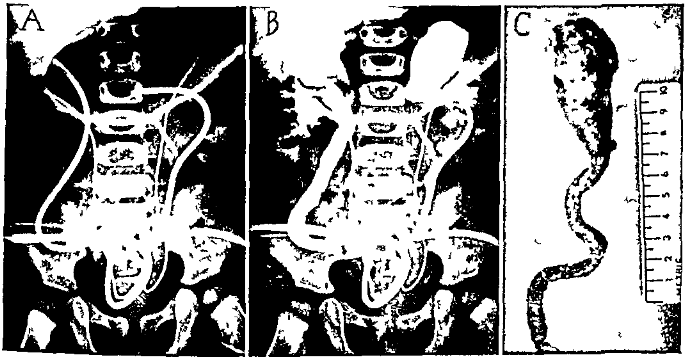

FIG 8 Case 7 *A* and *B*, on right, through open bladder No 5 ureteral catheter has been inserted through normal ureteral orifice going to normal half of left kidney, soft rubber catheter enters orifice where ureterocele has been excised and goes to hydronephrotic upper half of same kidney On left, small ureteral catheter goes through normal orifice to normal lower half of left kidney Large catheter has been passed to upper half of this kidney whose ureter originally ended in vagina Ureter has been severed from vagina and brought out through a stab wound *C*, specimen from subsequent left heminephro ureterectomy

grade pyelograms On cystoscopy, we noted a mass of mucous membrane folds almost filling the bladder whose exact nature could not be determined An opening, 1 cm in diameter, which appeared to be into a diverticulum, was seen among these folds Two normal ureteral orifices were noted, but only one could be neath which lie the splenic vessels which are ligated. The gastrosplenic and the lienorenal ligaments are divided which frees the spleen for removal.

The technique of splenectomy during left kidney operations is fairly simple. The peritoneal tear and splenic hemorrhage usually are obvious. Since the peritoneum is torn most often at the lienorenal ligament, the splenic vessels are seen as they enter the hilum of the spleen. Ligation of these vessels is best done by clamping about two inches proximal to the terminations of the splenic artery. The splenic pedicle should be tied at least twice for added safety, and the peritoneal rent closed as well as possible. If nephrectomy is done first the splenectomy is fairly easy. If a plastic operation is done on the kidney, splenectomy might be difficult and would require enlarging the peritoneal tear for additional exposure.

CASE REPORTS

Case 1. Mr. A. M., a 77 year old white man, was first seen on October 6, 1948, because of a feeling of intermittent fullness, pain and tenderness in the left upper quadrant for 1 year. He had passed blood and pus in his urine frequently for 2 years. He had been having frequency, nocturia, and difficulty in starting the urinary stream for over a year, and had had low grade fever for 1 month. There had been no surgery or serious illness previously.

Positive physical findings on admission to Jefferson Davis Hospital were: temperature of 102.4F; râles in bases of both lungs (particularly the left); marked abdominal distention; a tender, mobile mass in the left upper quadrant; complete ankylosis of the left hip joint, and a 1 plus enlarged benign prostate.

Hemoglobin was 9.5 gm.; red blood cells, 3.1 million, white blood cells, 15,750 with a differential showing a shift to the left. Urine had a specific gravity of 1.020, trace of albumin, negative sugar, 20–30 red blood cells per high power field and 3–5 white blood cells per high power field. Urine culture was positive for Aerobacter aerogenes. Nonprotein nitrogen was 27 mg. per cent, and Kline 4 plus.

Cystoscopy was unsatisfactory due to ankylosis of the left hip. There was a 1 plus enlargement of the prostate intra-urethrally and moderate trabeculations of the bladder. Neither ureter could be catheterized.

Kidney, ureter, and bladder showed an opacity throughout the left abdomen but no psoas shadow. Excretory urograms showed a normal right kidney but no excretion from the left. An aortogram was unsatisfactory since most of the dye entered the celiac axis.

On October 13, 1948, the left kidney was exposed through the usual loin incision. There were extensive adhesions around the markedly enlarged kidney. The kidney pedicle was isolated, clamped, cut, and tied. During the kidney dissection the peritoneum was opened inadvertently and an extensive laceration of the spleen was noted. This tear could not be repaired and since bleeding was very troublesome the spleen was removed. The large peritoneal defect was closed as completely as possible. The wound was closed in layers with No. 28 gauge stainless steel wire.

Postoperatively the patient's condition was poor and, in spite of transfusions of blood and plasma, death occurred twenty-four hours following operation.

Autopsy was denied. The pathology department reported severe pyelonephrosis of the left kidney with extensive perinephritis. The spleen showed passive hyperemia.

Case 2. N. J., a 69 year old colored man, was admitted to Jefferson Davis Hospital on September 9, 1951, complaining of abdominal fullness and a dull aching pain in his left side for about eight months. He had had bronchial asthma with exertional dyspnea for 10 years, and gave a positive history of gonorrhea and syphilis. For the past 6 weeks there had been loss of appetite, intermittent nausea, vomiting, and weight loss of 15 pounds.

Physical examination revealed a mass roughly 12 by 18 cm. in the left hypochondrium and loin. It moved with respiration, was firm and slightly tender. No other abnormalities were noted. Blood pressure was 120/80.

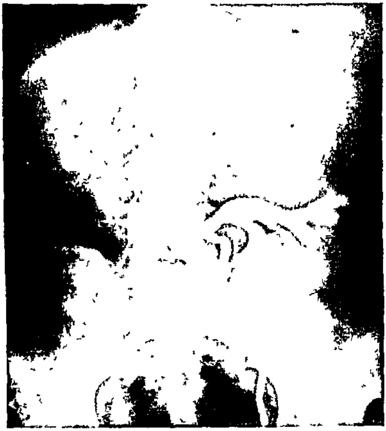

FIG. 1. Case 2. Pyelogram

Hemoglobin was 9.0 gm.; red blood cells, 3.8 million; hematocrit, 41 per cent; blood urea nitrogen was 7 mg. per cent.

Kidney, ureter, and bladder showed a density in the left upper quadrant. Following injection of the dye there was prompt excretion bilaterally. The right kidney and ureter were normal. There was elongation of the superior calyx of the left kidney which was displaced downward and rotated so that the pelvis and calyces lay almost horizontal. Cystoscopy showed grade I intra-urethral enlargement of the prostate with moderate trabeculations of the bladder. Retrograde pyelograms revealed essentially the same findings as the excretory urograms (fig. 1). A chest film was negative.

The patient was given 1000 cc blood preoperatively and on September 26, 1941, the left kidney was explored through a loin incision. Upon opening Gerota's fascia a large tumor mass was seen arising from the upper pole, measuring 5–6 inches in diameter. The entire mass and kidney were freed and the pedicle was clamped, cut, and tied. Inadvertently the peritoneum was opened during the dissection of the kidney and there was extensive bleeding from the spleen. The splenic pedicle was clamped, cut, and tied and the spleen removed. The peritoneum was closed with plain 00 catgut and the loin incision was closed in layers.

Grossly the specimen appeared to be an upper pole kidney tumor (fig. 2). However, it easily separated from the upper pole of the kidney below and the flattened adrenal above, and did not appear to arise from either organ. The final histological diagnosis was retroperitoneal fibrosarcoma (fig. 3).

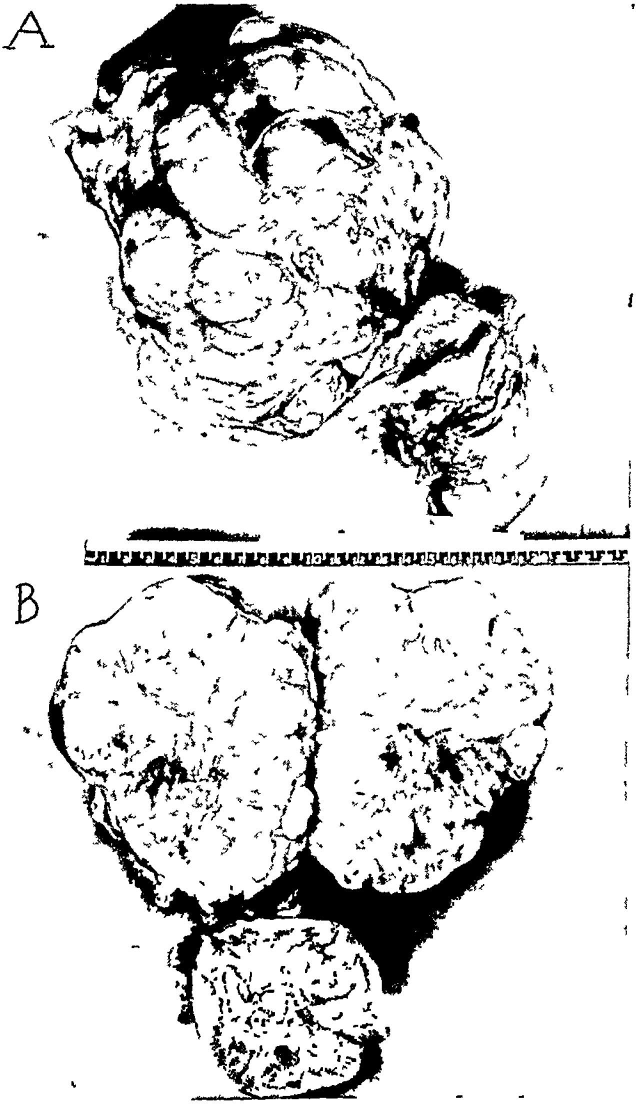

FIG. 2. Case 2. *A*, gross specimen. *B*, specimen on section

The patient had an uneventful postoperative course until the seventh day when he began to vomit and shortly thereafter went into shock. He had no pain. A bedside chest x-ray was negative. Hemoglobin was 10.5 gm. and hematocrit was 44 per cent. An electrocardiogram showed a sinus tachycardia of 140 with premature ventricular contractions, and suggested auricular enlargement. The patient was given adrenal cortical extract, 500 cc blood, and was digitalized. In spite of these supportive measures he expired within six hours of the onset of the unexplained attack. Postmortem examination was denied.

Case 3. G. T., a 50 year old colored woman, was admitted to Jefferson Davis Hospital on February 1, 1952. In 1922 she was treated for syphilis. In 1928 she had a colostomy for stricture of the rectum. It was reconstructed in 1938 and again in 1949. Six weeks before admission, the colostomy began to close. She began to vomit and lost weight. Three weeks before admission she contracted the "flu," with pain in the left lower chest posteriorly, and a productive cough.

Examination revealed a thin, emaciated colored woman who was acutely ill. Blood pressure, 100/70. Temperature, 102F. There was bronchial breathing, crepitant râles over the left lower chest posteriorly, with dulness and tenderness to percussion. The left lower quadrant colostomy was almost completely closed. Pelvic examination revealed numerous condylomata on the vulva, but a clean cervix. The rectum would not admit the little finger.

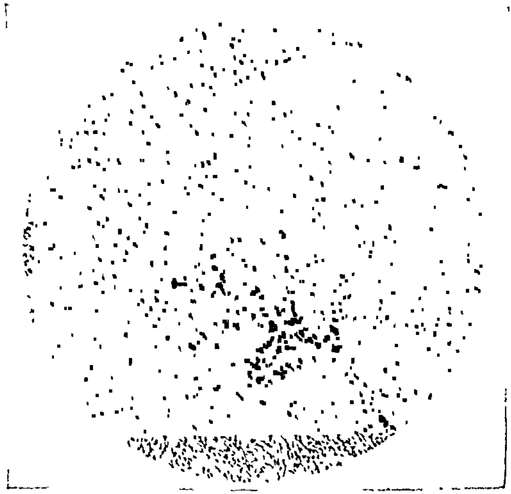

FIG. 3. Case 2 Photomicrograph

Hemoglobin was 3.9 gm. Red blood cells, 2 million, white blood cells, 10,200 with a slight left shift in the differential. Urinalysis showed acid urine, specific gravity 1.009, trace of albumin, 4 plus white blood cells and 1 plus red blood cells per high power field. The blood urea nitrogen was 27 mg. per cent, serum chlorides were 100 milliequivalent and the carbon dioxide was 65 volumes per cent. Serological tests were negative. A Frei test was positive.

The patient was given 1000 cc blood and the colostomy was incised and drained. A chest film revealed either consolidation or fluid in the left lower chest. [illegible] choscopy showed nonspecific inflammatory reaction in the left lower lobe bronchus. Papanicolaou stain of material aspirated was negative. Excretory urograms showed no function of the left and poor function of the right kidney. Cystoscopy revealed a very tight urethral stricture, no residual, and a bladder capacity of 150 cc. The bladder mucosa was normal except for the edematous and inflamed left ureteral orifice from which pus was seen to exude. Catheters were passed with ease. The right kidney urine was clear; 40 cc of pus was aspirated from the

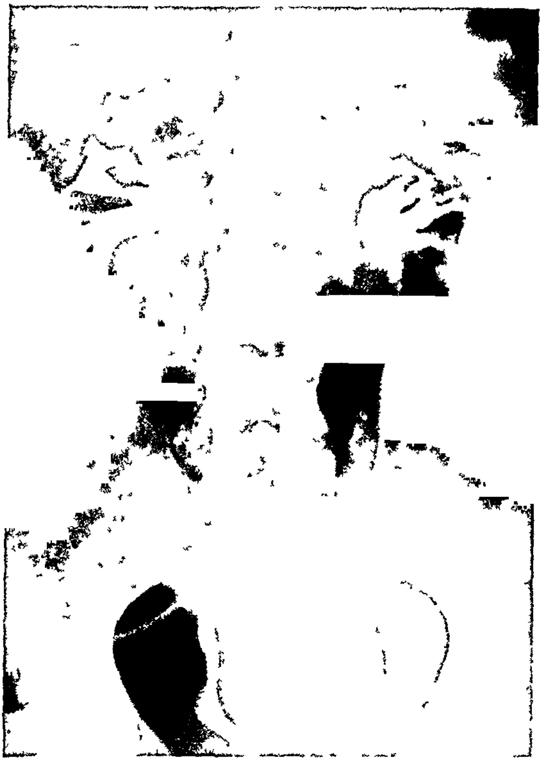

Fig. 4. Case 3. Pyelogram

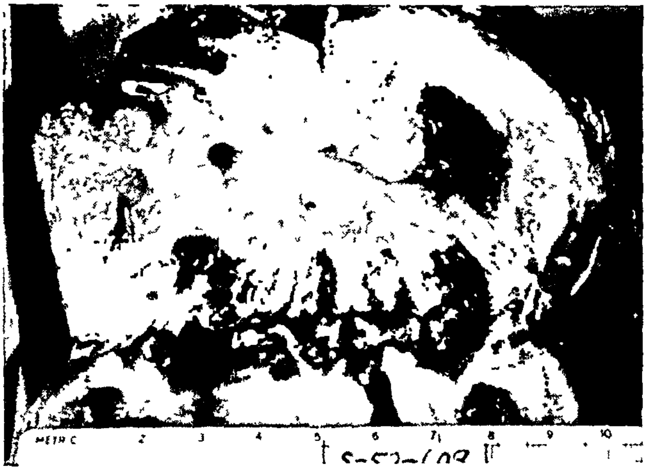

Fig. 5. Case 3. Gross specimen

left kidney. Indigo carmine appeared from the right kidney in four minutes in fair concentration but did not appear from the left in 30 minutes. Right pyeloureterograms showed very slight dilation of the calyces. The left kidney showed grade 3 hydronephrosis and an irregular, fuzzy pelvis (fig. 4). The ureter seemed to be involved in the same process. The bladder urine and left kidney urine culture showed Proteus and staphylococcus, while the urine from the right kidney was negative. A preoperative diagnosis of left renal tuberculosis was made in spite of numerous smears for acid fast bacilli being negative. After this diagnosis 50 cc of cloudy yellow fluid was removed from the left chest.

The patient was placed on streptomycin, para-aminosalicylic acid and was given another 1000 cc of blood. On February 27, 1952, through a left loin incision, extensive perinephritis was encountered and the ureter was never identified definitely. The peritoneum was entered but was not closed immediately. The upper pole of the kidney was soft, plastered to the diaphragm and was thought to be pyonephrotic. This mass of soft tissue was torn into and found to be spleen. It was densely adherent to the upper pole of the kidney but was gradually separated from it. The kidney was removed in the usual manner. The spleen continued to bleed so it was removed after its pedicle was clamped, cut, and tied. The peritoneum was closed and the wound was sutured in layers. The postoperative condition was uneventful. The blood urea nitrogen rose to 73 mg. per cent on the fourth postoperative day but returned to 40 where it stabilized. The patient was dismissed on the fourteenth postoperative day.

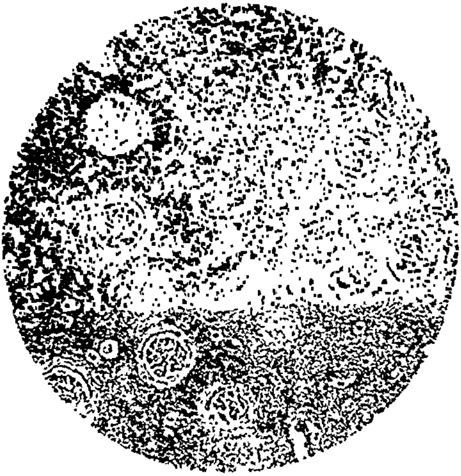

FIG. 6. Case 3. Photomicrograph

The gross specimen was thought to be tumor or tuberculosis (fig. 5). The histological sections showed severe chronic pyelonephritis with fatty replacement of almost the entire parenchyma, compatible with a diagnosis of renal lipomatosis (fig. 6).

DISCUSSION

In the past four years at the Jefferson Davis Hospital, the city-county institution, in Houston, Texas splenectomy has been performed along with left nephrectomy in 3 cases. During the same 4-year period 63 operations (table 1) were performed on the left kidney, of which 28 were nephrectomies. Statistically 4.7 per cent of left renal operations were complicated by splenic trauma and required splenectomy. However, such figures surely demonstrate the fallacy of statistics, for one of us (N.B.P.) in 14 years of urological residency and private practice has operated on only one such case (case 1).

The 3 cases reported were all difficult nephrectomies. Two were complicated by severe perinephritis, while the other was a large tumor. Two of the three patients died, one within 24 hours, the other on the seventh postoperative day, a mortality of 66⅔ per cent. However, splenectomy was not a contributory factor in these deaths. All operations were done by senior residents who were relatively inexperienced surgeons at the time. Desjaques et al.[3] reported over a 50 per cent mortality rate for combined nephrectomy and splenectomy in 46 cases of combined injury.

TABLE 1. *Summary of left renal operations, 48 months period*

TYPE OF OPERATION	NUMBER OF CASES
Nephrectomy	28
Nephrostomy	15
Nephrolithotomy	6
Pyelostomy	4
Perinephric abscess	3
Pyelotomy	2
Nephropexy	2
Pyelostomy	1
Pyeloplasty	1
Stab wound	1
	63

A contributing factor necessitating splenectomy was the severe perinephritic inflammation. In case 3 the spleen was tightly adherent not only to the left kidney but also to the tail of the pancreas. The close relationship of the spleen, stomach, and pancreas to the left kidney shows that these organs occasionally are involved in the perinephritic inflammatory process.

The question arises: Should a lacerated spleen be sutured or removed? Thorek[9] says that "while tamponade and suture still have their champions, splenectomy is coming constantly to the fore as the method of choice in the treatment of rupture of the spleen." Christopher[10] in his *Textbook of Surgery* does not mention suture for injury to the spleen, and other surgical authors say that only in the smallest of lacerations is repair justifiable Suturing is time consuming and not always successful, whereas splenectomy is relatively simple

SUMMARY AND CONCLUSIONS

The occurrence of surgical injury to the spleen during left renal surgery is discussed The anatomical relationships of the spleen and left kidney are reviewed and the surgical approach to the spleen is described Three cases are presented in which splenectomy was done with nephrectomy for nontraumatic lesions of the left kidney In this series, splenectomy was not necessary in the plastic or exploratory left renal operations, although conceivably splenic injury can occur during any type of left kidney surgery The possibility of injury to the spleen during difficult left renal surgery is very real and splenectomy is recommended when this unfortunate accident occurs

215 First National Bldg , El Paso, Texas (J D B)
801 Hermann Professional Bldg , Houston 25, Texas (N.B.P.)

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"LIGHT" PONTOCAINE FOR SPINAL ANESTHESIA IN RENAL SURGERY: A STUDY OF 175 PATIENTS

LEROY WILLIAM LEE AND EDWIN DAVIS, JR.

From the Departments of Urological Surgery of the Hospital of the University of Nebraska College of Medicine and the Clarkson Memorial Hospital, Omaha, Neb.

"Light" pontocaine is a solution for spinal anesthesia which allows for profound sustained anesthetic action free of untoward side reactions. By dissolving pontocaine crystals in triple distilled water (ampoules)* an agent for intrathecal administration, lighter than spinal fluid, is obtained. In the terminology of the anesthesiologist this is a "hypobaric solution." The idea of hypobaric agents for spinal anesthesia is not new. According to Lund and Cameron,[1] Pitkin in 1927 first introduced such a solution in "spinocaine." This drug, however, never enjoyed popularity.

The extent of spread of anesthetic solution in the subarachnoid space is determined for the most part by force of the injection (barbotage) and convection by gravity. It is difficult to control the former, but the latter may be controlled accurately by the relative specific gravity of the anesthetizing agent as compared to the specific gravity of the spinal fluid, hence the term hypobaric meaning lighter than spinal fluid.

The use of "heavy" pontocaine (hyperbaric) solution to produce low spinal anesthesia for various surgical procedures has proved to be popular in the United States. Its value in transurethral surgery was recently emphasized by Lee.[2] The value of light pontocaine (hypobaric) for controlled anesthesia is not well known at this time in the United States. Perhaps this is due to the recency of its introduction. From Canada comes a report by Lund and Cameron[1] who describe their results with hypobaric pontocaine in 175 general surgical patients and later supplement with a report of 1640 cases.[3] It is their conclusion that the drug can be used to advantage in all cases suitable for spinal anesthesia which require under 2 to 2½ hours of operating time. However, they had to supplement 22 per cent of their patients with intravenous Pentothal sodium by reason of prolonged operating time.

METHOD

In order to avoid supplemental anesthesia by any route except spinal it was felt that the continouus spinal technique of Lemmon could be modified to fit the requirements of renal surgery using hypobaric pontocaine. For details concern-

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Read at annual meeting, South Central Section, American Urological Association, Hot Springs, Ark., September 29, 1952.

* Winthrop-Stearns, Inc., N. Y., *supplied* 20 *cc ampoules containing* 0.1 per cent hypobaric pontocaine for this study.

[1] Lund, P. C., and Cameron, J. D.: Hypobaric pontocaine: A new technicque in spinal anesthesia. Anesthesiology. **6:** 565–573, 1945.

[2] Lee, L. W.: "Heavy" pontocaine for low spinal anesthesia in transurethral sugery. J. Urol., **64:** 750–751, 1950.

[3] Lund, P. C. and Rumball, A. C.: Hypobaric pontocaine spinal anesthesia, 1640 consecutive cases. Anesthesiology. **8:** 181–191, 1947.

ing continuous spinal anesthesia the papers of Lemmon[4] and Lemmon and Paschal[5] may be consulted. All that are needed to adapt the continuous spinal technique to the use of hypobaric pontocaine in renal surgery are a 20 cc Luer-lok syringe; a connecting unit consisting of stopcock, rubber tubing, and adapter; and a malleable steel spinal needle.* With these basic pieces of equipment the anesthesia technique herein described may be followed. (See figure 1.)

TECHNIQUE

Before coming to the operating room all patients for spinal anesthesia receive a barbiturate (such as Nembutal) and morphine. With the patient in the lateral position and mild Trendelenburg, skin anesthesia is obtained locally with 2 cc of 1 per cent Novocain solution to which has been added 0.5 cc of 1 per cent Neosynephrin. This is placed at the level of the third or fourth lumbar interspace. The No. 19 malleable steel continuous spinal needle is introduced intrathecally. The anesthetizing agent is prepared by dissolving 20 mg. of pontocaine crystals in 20 cc of triple distilled water. Twelve cubic centimeters of this 0.1 per cent hypobaric pontocaine (12 mg. of pontocaine) are injected into the intrathecal space through the Lemmon continuous spinal connecting unit. (See figure

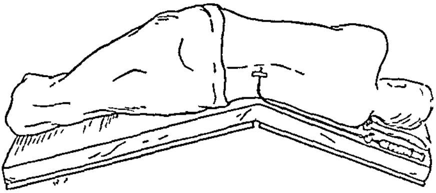

FIG. 1

TABLE 1. *"Light" pontocaine in renal surgery, 175 patients*

OPERATION	NUMBER OF PATIENTS
Nephrectomy	115
Pelviolithotomy	24
Ureterolithotomy (high)	16
Pelvioplasty and nephropexy	11
Nephrolysis and nephropexy	3
Ureterostomy	1
Exploration for adrenal tumor	1
Nephro-ureterectomy	3
Heminephrectomy	1
Postoperative mortality	None

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[4] Lemmon, W. T.. A method for continuous spinal anesthesia. Ann Surg , 3: 14–144, 1940.

[5] Lemmon, W. T. and Paschal, G. W.: Continuous—serial, fractional, controllable, intermittent—spinal anesthesia. With observations on 1000 cases Surg. Gynec & Obst., 74: 948–956, 1942.

* B-D Special needle. F 462LNR.

1.) Immediately after injection of the agent the patient is placed in lumbar kidney position with full break of table and elevation of rib elevator. Intravenous fluids (saline or 5 per cent glucose in water) are started in every case as a prophylaxis against fall in blood pressure. From the time of initial injection it usually takes 2 to 10 minutes for surgical anesthesia to develop. Anesthesia may be supplemented if necessary by injection of additional hypobaric pontocaine in increments of two or more cubic centimeters.

RESULTS

The method has been used in the past 3 years in a series of 175 patients without an anesthetic failure and without untoward side effects. By routinely starting intravenous fluids immediately after administering the anesthetic agent it was possible to control the blood pressure satisfactorily in every case. There were many patients with hypertension in this series.

Table 1 summarizes information as to operative procedure and number of each done with this anesthetic technique.

The usual operating time for these procedures ranged from 20 to 60 minutes although in a few instances surgery continued for 90 minutes. Initial dosage in each instance being 12 cc of hypobaric pontocaine (12 mg.), approximately 50 per cent of the patients needed supplemental injections of agent amounting from 2 to 8 cc to provide satisfactory surgical anesthesia. It is noteworthy that the profound anesthesia and relaxation of tissue provided by this anesthetic facilitated greatly the mechanics of surgical instrumentation.

CONCLUSIONS

A method of spinal anesthesia with "light" pontocaine is described which is admirably suited for renal surgery, in the lateral (lumbar) position, by reason of profound anesthesia of certain long duration without untoward side effects.

It is noteworthy that many of the patients reported in this study had hypertension. It may be that many serious drops in blood pressure were averted by reason of the routine use of intravenous fluids in conjunction with this anesthesia technique.

1436 Medical Arts Bldg., Omaha 2, Neb.

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RETROCAVAL (CIRCUMCAVAL) URETER ASSOCIATED WITH SOLITARY KIDNEY

VICTOR C LAUGHLIN

From the Department of Urology, Huron Road Hospital, Cleveland 12, Ohio

The peculiar position which the ureter assumes in this condition gives origin to a variety of terms to describe it, viz , retrocaval ureter, postcaval ureter, circumcaval ureter, deflected ureter and pre ureteric vena cava More properly, the deformity is classified as an abnormality of the vascular system, a point which is substantiated by embryological study The ureter, instead of passing lateral to the vena cava, passes behind it, partially encircles it for a short distance, and then pursues its normal course ventral to the vena cava, downward into the bony pelvis and thence to the bladder

In 1893, Hochstetter first described retrocaval ureter Mullen and Engel state that 55 cases have been reported Twenty one were discovered in dissecting room cadavers or at autopsies, thirty-four at surgery, and one was diagnosed by x ray but not operated upon These authors add one of their own

The vast majority of cases have occurred in males, a comparative few have been reported in females In every instance except one, the acardiac monster of Gladstone, the lesion has occurred on the right side In Gladstone's case, the lesion was bilateral In no case reported to date has the lesion been found associated with a solitary kidney The case we are reporting suggests this type of deformity and brings the total number of reported cases to fifty seven There are a number of unreported cases

The apparent rarity of this condition must be based upon unfamiliarity with its existence The pyelographic course of the ureter is so typical that once seen, it is not easily forgotten

EMBRYOLOGY

Simply stated, the embryological explanation of this condition lies in the development of the venous system, principally the vena cava, rather than the abnormal development of the ureter

In the normal embryo, the permanent kidneys, having formed in the pelvis, ascend cranialward After passing the bifurcation of the aorta, they encounter on either side the trunk of the postcardinal veins The kidneys pass medial to these veins and then shift laterally behind them so that the ureter virtually becomes wound around the posterior cardinal veins Because of the rich anastomosis of veins in the area, the kidney and ureter pass through three complex venous rings during their ascent Normally, certain of these veins function only temporarily, then disappear Others persist to adult life

Thus, in man, if the ureter lies in front or lateral to the vena cava, it is the supracardinal vein which has persisted, whereas, if the ureter lies behind the inferior vena cava, the posterior cardinal vein has persisted Should both the

Accepted for publication February 3, 1953

supracardinal vein and posterior cardinal vein persist, the cava will be double and the ureter will pass between the two divisions. Therefore, failure of atrophy of the posterior cardinal system of veins is the accepted embryological explanation of this anomaly.

CLINICAL FEATURES

Unfortunately, there are no symptoms pathognomonic of postcaval ureter. Usually the symptoms are those of obstruction, sometimes complicated by the symptoms of infection or stone. All of the surgical cases have had hydronephrosis. This was the reason for operation. Life is not incompatible with this condition. It is probable that, if sufficient time elapses, hydronephrosis from ureteral compression would occur in every instance. The mechanism may be compression alone or by kinking or stricture, due to the anomalous course which the ureter assumes. Symptomatology has varied from no symptoms at all to severe renal colic with sharp pain radiating along the ureter. Frequency following each attack may occur. Nocturia is often seen. Hematuria, gross or microscopic, has been a fairly constant feature. Pyuria has been frequent with secondary infection or stone. Age is a factor. It has not been reported clinically below the age of twelve, principally because the time element for the development of hydronephrosis is important. Hydronephrosis is the rule, therefore, in older patients.

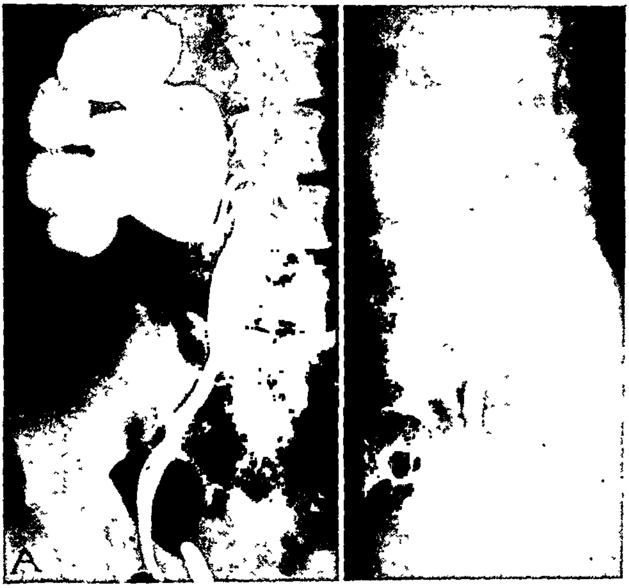

FIG. 1

Frequency may intensify the symptoms and hasten the obstructive pathological process. This happened in our case.

Hypertension reported has apparently been a coincidental finding, associated with other pathological change, such as nephrolithiasis, etc. Hematuria and loin pain in the cases reported have existed for variable periods of a few weeks to seven years.

DIAGNOSIS

Postcaval ureter should be considered a possibility in all cases of right hydronephrosis. Its x-ray features are so distinctive as to be almost pathognomonic; therefore, much diagnostic reliance must be placed upon x-ray studies for the proper preoperative diagnosis and subsequent corrective surgery. Surgeons employing the lumbar renal incision may not observe the entire course of the ureter and may miss the obstructive factor at the vena cava.

The distinctive roentgenographic features are as follows: Anterior ureteropyelography reveals hydronephrosis with a very long proximal segment of the ureter involved (fig. 1, *A*). The ureter is dislocated medially to or beyond the midline, beginning with the third, fourth, or fifth lumbar vertebrae. The resultant redundancy from obstruction and hydronephrosis produces a characteristic hook and a distinct sickle-shape or S-curve is imparted to the ureter. After the ureter has passed around the cava, it comes downward into the pelvis with a normal course and caliber. Its medial portion is not dilated. In oblique and lateral views (fig. 1, *B*) the retrocaval ureter hugs the spinal column instead of falling away from it. It becomes anterior to the vertebral bodies at about the third lumbar vertebra. This third dimension view is an added measure in the diagnosis and almost pathognomonic in a high percentage of cases.

SURGERY

Surgical therapy has consisted of nephrectomy in far advanced cases and attempts at renal conservation in the cases with a partially damaged kidney. In order to avoid postoperative stenosis of a re-anastomosed ureter, better surgical results have followed the division of the hydronephrotic segment above the ureteropelvic outlet, carefully withdrawing the detached segment from behind the vena cava, and re-anastomosing the pelvis. Thus, the ureter is brought anterior to the vena cava. Division of the pelvis at a point above the insertion of the ureter provides a tube of greater diameter, thus lessening the possibility of postoperative stricture. Obviously, in some instances, the surgeon may be forced to resect a constricted portion of the ureter.

Ten instances of successful surgical repair have been reported. Certain dangers and difficulties and to be considered in the repair. Removal of adhesions at the uretero-vena caval attachment may strip the local ureteral blood supply and interfere with proper healing of the anastomosis. The vena cava may be torn where adhesions to it and the ureter are dense. This was formerly considered a serious complication. Now, elective vena caval interruption is not an unusual procedure.

CASE REPORT

Mrs. L. B., aged 36, white, case No. 51-8517, was admitted to the obstetrical department of Huron Road Hospital in East Cleveland, Ohio, by Dr. Samuel Vinci and Dr. Jess J. Woodworth, on October 11, 1951. Chief complaint: "Pain in right flank, 18 hours duration, and no urine in bladder since onset of the pain." The patient was 7 months into her fifth pregnancy, which had been uneventful except for ankle edema. Approximately 18 hours before admission, the patient had a sudden onset of severe pain in the right flank and loin associated with nausea. The pain tended to remain steady and occasionally radiated to the genitalia. No urine had passed since the onset of the pain.

Blood pressure, 120/80. Temperature, 36.2. Pulse, 96. The patient was apprehensive and abnormal findings were limited to the abdomen which was enlarged, consistent with a seven-month pregnancy. There was marked tenderness to punch percussion over the right costovertebral angle with questionable muscle guarding below the right costal margin.

Laboratory findings: The blood chemistry was as follows: Nonprotein nitrogen 47.5 mg/100 cc. Uric acid 5.6 mg/100 cc. Blood urea nitrogen 26.0 mg/100 cc. Hemoglobin 68.4 per cent; red blood cells 3,710,000; white blood cells 15,950; neutrophils 88; eosinophils 1; lymphocytes 6; monocytes 5. Slight hypochromia; slight anisocytosis; and slight left shift.

On the obstetrical service, after finding no urine at two catheterizations, the patient was given sedation, antispasmotics and intravenous fluids. The urological service was called the night of admission. The patient was cystoscoped, retrograde pyelograms made, massive pyelectasis discovered, the course of the ureter delineated, and a diagnosis of retrocaval ureter made. A very careful search failed to reveal a left ureteral orifice. A No. 6 olive-tip catheter was left in the right renal pelvis for decompression. The bladder was left empty. One hour after the procedure, the patient voided profusely from drainage around the catheter. The following morning the ureteral catheter was removed. The patient continued to void.

By the fourth hospital day, the blood chemistry was normal. The urine was still low in specific gravity with red and white blood cells and the sedimentation rate was 74 mm., dropping later to 58 mm. Excretory urograms failed to show any evidence of the presence of a left kidney. They continued to show the persistent pyelectasis on the right side. The patient was discharged on the eighth hospital day in good condition, voiding very well. She had received antibiotic supportive therapy. The fetal heart rate remained normal throughout the hospital stay.

Two months later, on December 6, 1951, the patient was re-admitted and delivered of a normal infant. The delivery was uneventful. On the eighth day postpartum, the cystoscopy was repeated under local anesthesia. The mucosa of the bladder was normal except in the region of the right ureteral orifice where it appeared moderately inflamed and slightly edematous. The orifice was patent. Using a Woodruff engaging tip catheter and 40 per cent skiodan, by gravity only, a pyelo-ureterogram was made which showed some slight reduction in the degree of pyelectasis, (fig. 1, *A*). A No. 4 olive-tip catheter was passed to the renal pelvis and a lateral pyelogram made (fig. 1, *B*).

Again, a careful search for the left ureter failed to disclose it. Oxygen 1000 cc was introduced retroperitoneally and a series of x-rays made. A third set of excretory urograms were taken. No evidence of a left kidney was present on any of those films The patient had no symptoms Five children and a husband depended on her She declined surgical correction of the deformity We are waiting patiently Further developments will undoubtedly change her mind

SUMMARY

A case of circumcaval, postcaval, or retrocaval ureter has been reported probably the fifty-seventh Possibly it is the first reported associated with a solitary right kidney No kidney could be demonstrated on the left side by non operative means

Retrocaval ureter should always be considered in cases of right hydronephrosis, especially where the proximal ureteral segment is long and dilated and the course of the ureter extends to the midline or beyond

The S-shape deformity in the proximal ureter is characteristic

The symptomatology is that of the obstructive lesion which develops complicated or not by infection or stone

Pregnancy hastens the development of the obstructive changes and, therefore, the symptoms likewise

Surgical procedure of choice, when surgery is performed, is division of the hydronephrotic segment above the ureteropelvic junction, removal of the ureter from behind the vena cava and re-anastomosis

1831 Forest Hills Blvd , East Cleveland 12, Ohio

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URETEROVAGINAL FISTULA

REXFORD G. CARTER

Injuries to the ureter as a result of pelvic surgery are not uncommon. These unfortunate accidents happen to the experienced surgeon and gynecologist as well as to the novice. There is not much difference of opinion as to the cause of the accident, but there is considerable difference of opinion among surgeons, gynecologists, and urologists as to the best course to pursue once urinary leakage has occurred following such pelvic surgery.

Most gynecologists and surgeons, including those who have written texts on the subject, feel that a course of watchful waiting is justified. They believe that a large percentage of these cases, approximately 50 per cent, will heal spontaneously within a period of time. The fallacy of this reasoning will be shown later. On the other hand, the urologists feel that the problem is a challenge to the preservation of renal tissue and that every effort should be made to save the damaged kidney and ureter if possible. However, this opinion is not universally held by urologists and some writers of recent textbooks have taken the position that one-half or more will heal spontaneously and that nothing is lost by watchful waiting.

An examination of the basic facts involved, including the altered anatomy and physiology of the damaged tissues, cannot fail to support the theory that prompt intervention is necessary and desirable if the best interests of the patient are to be served. Anyone who has investigated these patients following the initial injury, whether it is a few days or several weeks later, is impressed by the fact that a normal kidney and ureter do not exist in the presence of a ureterovaginal fistula. The injury produces some degree of obstruction. As time goes on, the obstructive factor increases and infection appears. As a result of these events, the kidney is damaged and the damage becomes progressive. If a policy of watchful waiting is pursued for a period of two to three months, as advocated by many authors, the kidney will cease to function and the fistula will stop draining. This, no doubt, is the mechanism of the so-called spontaneous cures. It is true that the patient is cured in that she no longer leaks urine through the vagina. However, in most cases she does not realize and is not informed that she has only one kidney left.

This injury is due almost exclusively to some form of hysterectomy. A few cases occur as a result of difficult forceps delivery. The most frequent cause is abdominal hysterectomy followed closely by vaginal hysterectomy. During a ten-year period from 1940 to 1950, 35 cases were encountered in the Mayo Clinic. The over-all incidence from collected series in the literature is about four-tenths of one per cent of all hysterectomies. Newell and others reporting on a 15-year period at Barnes Hospital showed an incidence of 1 case in 188 hysterectomies. Moore reports a much higher incidence of injury, stating that ureteral ligation occurs in from one to three per cent of all operations on the female genital organs.

Read at annual meeting, South Central Section, American Urological Association, Hot Springs, Ark., September 29, 1952.

The injury occurs most frequently during the removal of large intraligamentous fibroids where the normal course of the ureter is considerably distorted

The second highest incidence is seen following vaginal hysterectomy, and thirdly, the radical type of hysterectomy or Wertheim procedure is the cause of some accidents However, in the latter case, the surgeon is usually on the lookout for the ureter and is more conscious of its presence and possible injury The injury may be caused by temporary clamping of the ureter but more often by catching the terminal portion of the ureter in a suture The damage usually occurs to the terminal 5 to 8 cm of the ureter In some cases the surgeon is aware that the ureter has been cut and this is the ideal time to attempt a repair An end to end anastomosis over a ureteral catheter or synthetic tubing is successful in a high percentage of the cases and is a simple procedure which can be easily and quickly done

Some surgeons have confessed to tying the ureter and dropping it back into the abdomen in such cases This is mentioned only to be condemned, as in most cases the condition of the kidney on the other side is not known The English surgeon, Bland-Sutton, emphasized the importance of dealing with the cut ureter at the time He pointed out that "kidney tissue is very precious Many persons get on very well in the world with very little brains and some with none at all, but no one can live without a certain amount of kidney" If the ureter is tied and dropped back, probably nothing will happen providing the opposite kidney is normal and the affected kidney is not infected However, should some infection be present in the obstructed kidney, a stormy postoperative course will ensue In any event, this is a needless sacrifice of what is usually a perfectly normal kidney

There has been considerable controversy over the advisability of using ureteral catheters preoperatively Many surgeons and gynecologists feel that it is unnecessary and some have stated in print that their use is unjustified However, most men feel that any help in a difficult hysterectomy is worthwhile, and preoperative ureteral catheterization is a harmless procedure which may be of real help to the surgeon

The symptoms of ureteral injury usually appear during the period of from three to ten days following operation If both ureters are completely occluded, the patient will pass no urine at all following the operation and none will be obtained upon catheterization This, of course, is an urgent emergency and requires immediate treatment In the past, many of these cases have been treated by deligation This procedure is attended by a very high mortality rate and has been reported to be as high as 40 to 50 per cent A much safer procedure is to do a unilateral nephrostomy or even a bilateral nephrostomy if the situation is grave This procedure will establish good renal drainage with an improvement in renal function After the patient's condition has improved sufficiently, a diagnostic survey can be made However, in most cases the injury is unilateral The ureter is either caught in a clamp or in a suture and a period of a few days is necessary before necrosis and sloughing occur Once the leakage of urine begins, it quickly finds its way to the outside by the easiest means In most cases this is through the suture line in the vault of the vagina These patients will void normally and at the same time leak constantly from the vagina. If a bladder injury is also present, the patient may not void at all with all of the urine leaking through the vagina. One may readily conclude that a vesicovaginal fistula is present and this is indeed the case. However, in these cases the ureteral injury with fistula formation may also be present. There are a few cases where both ureters are injured. In such cases some of the urine from one ureter may pass into the bladder and be voided normally while another portion of it leaks through the vagina. The other side may be more severely injured with most of the urine going into the vagina. Such situations only add to the difficulty in arriving at the correct diagnosis.

The diagnosis can be made after careful and complete urological investigation. The first procedure and often the most valuable one is the intravenous urogram. If only one ureter is injured, the normal kidney and ureter will be well demonstrated by this procedure. The injured side may show some delay in concentration of the dye and may show some dilatation of the ureter and renal pelvis. Where the damage is severe or has existed for a considerable period of time, the injured kidney may not show any function whatever. Cystoscopy should then be done and a careful search made for a bladder injury. Small vesicovaginal fistulas may not be readily apparent on examination and the bladder should be filled with a colored dye and a sponge placed in the vagina. If none of the color appears in the vaginal urine after a period of several minutes, it can be safely assumed that no bladder injury is present. The injured side will usually show obstruction to the passage of a ureteral catheter. In some cases, after considerable manipulation, a catheter may be passed beyond the injury and up to the renal pelvis, or in rare instances into the vagina. However, in a majority of cases the ureter is obstructed from 3 to 5 cm. above the ureteral orifice and no urine can be obtained from this side. Dye injected through the catheter very rarely will succeed in visualizing the upper ureter and kidney. In a few instances the dye can be seen passing through the fistula into the vagina. Intravenous dye can then be given to estimate the function of both kidneys. Usually the good kidney will excrete the dye promptly and in good concentration. If the injured side is excreting any dye at all, it will not be seen in the bladder. However, a sponge placed in the vagina and left for awhile will usually show the presence of some colored urine. In a small percentage of cases, it is possible to introduce a ureteral catheter through the vaginal fistula up the ureter to the kidney. If one is fortunate enough to accomplish this, a retrograde pyelogram can be obtained and a much better estimate of the function on the damaged side obtained.

Once the diagnosis is made, one is confronted with the problem of adequate treatment and the time element becomes very important. If it is felt that the damaged kidney is beyond salvage or if the injury is too high to permit any of the usual methods of repair, nephrectomy is indicated. In such cases immediate operation is not mandatory. The vaginal drainage can be permitted to continue for an indefinite period and may stop spontaneously as renal function ceases. If, on the other hand, the decision is made to salvage the kidney, early operation is necessary.

If the injury is within the lower 10 cm of the ureter, some type of repair can usually be accomplished If it is above that point, the proximal ureter is usually too short to re-implant into the bladder by any of the usual methods The only alternative is to transplant the injured ureter to the opposite ureter or to the large bowel These procedures are rarely indicated if the opposite kidney is normal Deligation of the ureter in these cases is rarely successful because considerable damage has already been done to the ureteral wall and drainage following deligation is usually not adequate Moore has reported more success with deligation However, his procedure differs from most in that the urologist manipulates the catheters through a cystoscope while the surgeon is exploring the abdomen to ascertain the point of obstruction and it is done early In some cases where the injury is slight, one may be fortunate enough to pass a catheter through the obstruction up to the renal pelvis In such cases the catheter should be left in place for a week or more and some of these fistulas will close This method should be given a fair trial if it is possible to pass a catheter from the bladder to the kidney on the affected side

There are several methods of repairing this condition and all consist of some type of transplant of the proximal end of the ureter into the bladder The approach should be retroperitoneal rather than through the peritoneal cavity This can usually be done without much difficulty and at the same time avoid the scarring and adhesions present at the site of the previous operation In most cases the distal portion of the ureter between the bladder and the fistula will be found to be embedded in dense scar and incapable of mobilization and further use However, there are exceptions and in some cases the distal segments of the ureter may be used for anastomosis The proximal portion of the ureter should be dissected as far downward as possible to its entrance into the fistula It can be severed at that point and re-implanted into the bladder where the point of contact is the easiest and with the least tension

It is generally felt that the lower the ureter is implanted into the bladder, the better the results will be The procedure which should produce the best functional result was described by Patton in 1939 He recommended dilating the intramural portion of the ureter and pulling the cut end of the severed ureter through this portion, the cut end then being sutured to the inner wall of the bladder This method preserves the normal course of the ureter through the bladder wall and also preserves the sphincter at the terminal end of the ureter if such sphincter actually exists Counseller and others have stated that re-implantation of the ureter into the dome of the bladder usually results in failure due to the fact that the ureter stands open and that regurgitation occurs It has been more recently shown that the incompetent ureter is not due to lack of a sphincter at the ureteral opening, inasmuch as many gaping ureteral orifices are seen wherein no regurgitation occurs If the muscle wall of the ureter is competent and normal peristaltic movements occur, regurgitation will not occur whether the ureteral meatus is open or closed Many good results have been reported from implanting the ureter into the dome or upper portion of the bladder

Four of these cases came to my attention within a period of 1 year. In two of the cases, nephrectomy was selected because of reasons which will be given in the case reports. In the other 2 cases, repair of the injured ureter was accomplished.

CASE REPORTS

Case 1. A 46 year old white woman had a hysterectomy for a large intraligamentous fibroid. Four days following the operation, she began to pass fluid from the vagina. During the next 2 weeks she continued to pass fluid and had a few ill-defined pains in the left flank and left lower quadrant. She was dismissed from the hospital but continued to pass urine constantly until seen 8 weeks following the original operation. At that time, an excretory urogram showed normal function of the right kidney and no dilatation of the ureter. No dye was excreted by the left kidney. On cystoscopic examination no defect could be demonstrated in the bladder. A catheter was passed to the right kidney without difficulty. On the left side, the catheter passed for a distance of 8 cm. and could not be passed beyond that point. No urine was obtained from the catheter and no dye could be injected upward into the kidney. None was seen passing into the vagina. A retrograde pyelogram showed a normal right kidney and blockage of the catheter on the left side. Due to the apparent lack of function of the left kidney, it was decided to do a nephrectomy on this patient. Accordingly, the left kidney was removed and showed an advanced degree of pyelonephritis with considerable dilatation of the renal pelvis and calyces.

Case 2. A 41 year old white woman was operated upon for carcinoma of the left ovary. A very extensive procedure was carried out and it was the feeling of the surgeon at the time that possibly some malignant tissue was left. Ten days following the operation, she began to pass urine from the vagina. She had intermittent pain in the left flank and left lower quadrant. She was seen 6 weeks following this procedure at which time she was undergoing extensive x-ray therapy. An excretory urogram showed good function on the right side, no function on the left. Following this procedure, cystoscopy was done. No defect in the bladder was demonstrated. There was no leakage of fluid into the vagina. A catheter was passed to the right kidney without difficulty. On the left side, the catheter passed for a distance of 5 cm. but was blocked at that point. Retrograde pyelogram showed the right kidney to be normal. On the left side, dye could not be injected into the kidney but passed through the lower portion of the ureter into the vagina. Figure 1 shows this very clearly. Indigo carmine was given intravenously and appeared promptly on the right side. No dye appeared from the left ureter and a sponge was left in the vagina for a period of 30 minutes and showed no coloration whatever. Apparently the left kidney had no demonstrable function. Due to this apparent lack of function as well as the unfavorable prognosis, it was decided that nephrectomy would be the best procedure. Accordingly, that operation was done. When the kidney was removed, it was found to have an advanced degree of hydronephrosis and pyelonephritis.

Case 3. A 26 year old white woman had a hysterectomy and right oophorectomy for relief of a degenerating fibroid. Following operation she had pain in the left flank for a few days and 3 weeks after operation began to pass urine from the vagina although voiding normally at the time. An excretory urogram showed good function on the right side. Fair function was demonstrated on the left side and there was a moderate degree of hydronephrosis. The left ureter was not visualized. On cystoscopic examination, the catheter was passed to the right kidney without difficulty. On the left, the catheter was blocked 2 cm. from the ureteral orifice. There was no evidence of vesicovaginal fistula (fig. 2, *A*).

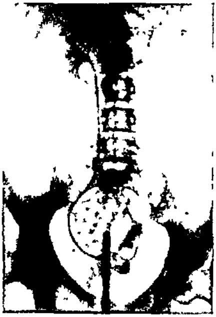

Fig. 1. Case 2. Normal right retrograde pyelogram. Extravasation of dye in lower portion of left ureter.

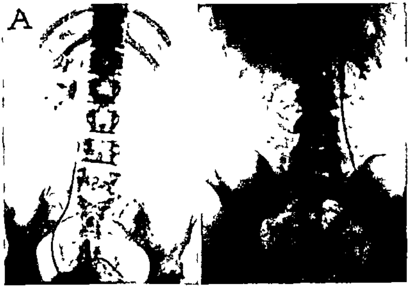

Fig. 2. Case 3. *A*, right retrograde pyelogram. Catheter blocked in lower left ureter. *B*, left retrograde pyelogram 6 weeks after repair.

Since the injury on the left side appeared to be quite low and there was still a fair degree of function left in the kidney, repair was elected. At operation, the left ureter was found to be moderately dilated and ended in an inflammatory mass just above the bladder. The distal portion of the ureter could not be located. The proximal portion of the ureter was divided where it entered the fistula and re-implanted into the upper posterior wall of the bladder without tension. Figure 2, *B* is a retrograde pyelogram made 6 weeks following operation and shows a normal left kidney. The patient was seen 1 year later.

Excretory films made at intervals of 5, 15, and 45 minutes demonstrated a normal kidney with good function on the left side, no ureteral dilatation, and a normal bladder outline with complete emptying of the kidneys.

Case 4. A 48 year old white woman was operated upon for multiple large fibroids. During the course of the operation, the right ureter was cut completely across. It was immediately recognized by the surgeon who repaired the ureter by an end-to-end anastomosis over a ureteral catheter, one end of which went up to the renal pelvis and the other end was left in the bladder. Following operation the lower end of the catheter was brought through the urethra through a cystoscope. Ten days after operation, urine began leaking through the vagina. It was felt of course, that the fistula involved the damaged right ureter. The patient was seen 5 weeks following the original operation at which time an excretory urogram showed a fairly normal kidney and ureter on the right with good function, but it showed a small amount of extravasation of the dye from the lower ureter. No function was demonstrated on the left side. Cystoscopic examination was then carried out. A catheter passed to the right kidney without difficulty. On the left side, the catheter was blocked about 3 cm. from the orifice. No urine was obtained, and no dye could be injected into the kidney. The pyelogram made on the right side showed a normal kidney and upper ureter. A filling defect was seen in the lower ureter, and there was extravasation of a small amount of dye at this point.

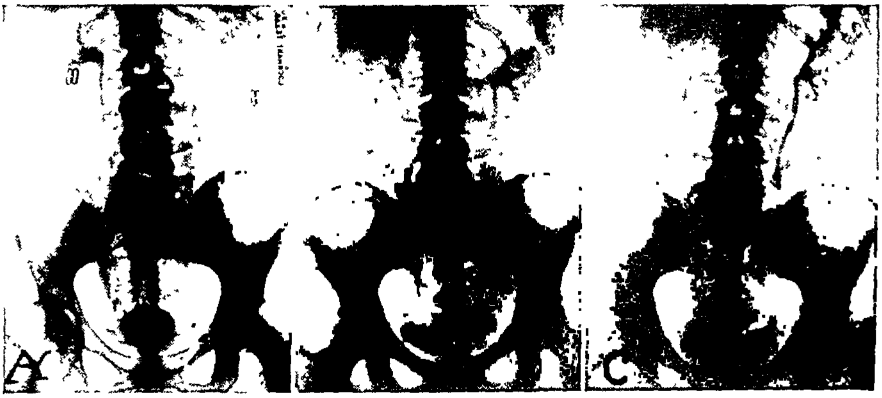

FIG. 3. Case 4. *A*, retrograde pyelogram shows extravasation from lower end of right ureter. Impossible to catheterize left ureter. *B*, excretory urogram 2 months following repair. Good function on both sides. No hydronephrosis. *C*, retrograde pyelogram 3 months following repair shows normal kidney and left ureter.

Figure 3, *A* demonstrates for the first time the true status of this patient. She apparently had a well functioning anastomosis on the right side with possibly a small amount of leakage but no obstruction. There was undoubtedly an injury to the lower left ureter with most of the urine from this kidney going into the vagina. A decision was made to attempt a repair on the left side even though no function was demonstrated in the left kidney. The deciding factor here was the presence of an injury on the right side which might produce future obstruction with consequent loss of function. At operation, the proximal ureter was located without difficulty and found to be moderately dilated. It was dissected down to its point of entrance into the fistula and severed at that point The cut end was then implanted into the bladder near the dome with very little tension Following operation, the urinary drainage from the vagina was considerably decreased but did not cease entirely Five days following the operation, the patient was given indigo carmine intravenously. The dye appeared promptly in the vaginal urine which indicated it was probably coming from the right side as this had the better function The bladder urine showed the appearance of the dye in fair concentration after about ten minutes which indicated good function of the transplant on the left side Two weeks following operation, vaginal leakage ceased, the wound was healed and the patient was symptom free Two months following operation, an excretory urogram (fig 3, *B*) showed good function of both kidneys and no evidence of hydronephrosis Cystoscopy was done and both ureteral orifices were seen to be functioning normally Indigo carmine given intravenously appeared from both sides in 4 minutes in good concentration A left retrograde pyelogram (fig 3, *C*) showed a normal kidney and ureter

This last case demonstrates how much renal function can be salvaged when good drainage is provided The final result shows an apparently normal kidney whereas no function was demonstrated preoperatively This case also effectively illustrates the hazard of tying a cut ureter and dropping it back into the abdomen Had the surgeon done so in this case with an unrecognized obstruction of the other ureter, the patient probably would not have survived

SUMMARY

Four cases of ureterovaginal fistula are presented These cases demonstrate the problems presented by this condition, and two of the cases show the degree of renal function that can be maintained by early diagnosis and treatment In most of the cases reported to date, the renal mortality rate is approximately 50 per cent If these patients were seen earlier by the urologists and adequate diagnoses were made, the incidence of nephrectomy could be lowered considerably

1709 San Antonio St., Austin, Texas

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THE CASE FOR EARLIER CYSTECTOMY IN CARCINOMA OF THE URINARY BLADDER

JUSTIN J. CORDONNIER

From the Department of Surgery, Washington University School of Medicine, St. Louis, Mo.

Perhaps the most controversial subject in the field of Urology in the last 10 years has been the role of total cystectomy with ureterosigmoid anastomosis in the treatment of carcinoma in the urinary bladder. When such authors as Colby[1] and Jewett[2] condemn the procedure as almost valueless, one feels that a careful evaluation of all available data should be made in an effort to find the true place of this procedure as a method of treatment. Although I do not believe that all cases of carcinoma of the bladder should be treated by radical means, it is my firm belief that radical total cystectomy with ureterosigmoid anastomosis, done at an earlier date than heretofore, over the years will improve the end results in the treatment of carcinoma of the urinary bladder. In my opinion, one of the principal reasons for the over-all poor results following cystectomy is the fact that most urologists reserve this procedure for advanced cases of carcinoma with a high degree of malignancy, or for those cases in which all other methods have failed. Certainly as long as this type of selection is carried out, statistics are going to continue to be poor. With the advent of improved methods of ureterosigmoid anastomosis, and modern chemotherapeutic agents, cystectomy can be recommended at an earlier stage and in this way improve both the mortality and morbidity in the treatment of carcinoma.

To date, our series consists of 69 cases. Three patients died during the immediate postoperative period, for an operative mortality of 4.3 per cent. All others left the hospital under their own power. Included in the series were many extremely poor operative risks. Operation has been refused to no one where it has been believed that the patient could withstand the immediate effects of surgery. It is our belief that the degree of palliation obtained following ureterosigmoid anastomosis, even though it is impossible to remove the bladder because of inoperable carcinoma, is well worth the operative procedure.

Late mortality is shown in table 1.

Included in the 4 to 5 year survival group are 3 patients on whom ureterosigmoidostomy was done for nonmalignant disease. All three of these are living and in comparatively good health. In the 4 to 5 year survival group are included two fairly far advanced cases. One patient had an undifferentiated transitional cell carcinoma, which had penetrated into the deepest layers of the bladder wall. The other presented recurrence with superficial muscle invasion following what was considered to have been an adequate partial cystectomy for an infiltrative lesion

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Read at annual meeting, South Central Section, American Urological Association, Hot Springs, Ark., October 1, 1952.

[1] Colby, F. H. and Kerr, W. S. Jr.: Carcinoma of the bladder: Evaluation of total cystectomy and other methods of treatment. New Eng. J. Med. **244:** 504–506, 1951.

[2] Jewett, H. J.: Carcinoma of the bladder: Treatment and prognosis. South. Med. J., **43:** 661–667, 1950.

on the dome of the bladder All other survivors in the group had grade 2 tumors with minimal penetration, cystectomy having been performed because of either multiplicity or rapidity of recurrence of the lesion

In the 3 to 4 year survival group were 2 cases of advanced carcinoma One presented a grade 4 lesion with invasion through all layers of the bladder The patient is still alive with no clinical evidence of recurrence The second had a grade 3 lesion with penetration through the entire bladder wall with tumor cells present in the lymphatics

The surprising length of survival in several cases which were considered hopeless at the time of surgery emphasizes the necessity of at least making an attempt to obtain a cure rather than abandoning the patient to simple palliation

TABLE 1

	JAN 48–49 4–5 YEAR GROUP	JAN 49 50 3–4 YEAR GROUP	JAN 50 51 2 3 YEAR GROUP	JAN 51 52 1 2 YEAR GROUP	JAN 52 PRESENT 0–1 YEAR GROUP
Alive	10	7	7	5	6
Dead	15	10	6	3	0

Total alive 35—dead 34

TABLE 2

Dead

	GRADE OF TUMOR (BRODERS CLASSIFICATION)		
	Grade 2	Grade 3	Grade 4
Number	10	7	9
Average survival	17 months	5 months	9 months

*Depth of Penetration**

	1 & 2	3	4
Number	6	5	3
Average survival	13 months	5 months	8 months

* 1 & 2—Mucosa and superficial muscle invasion 3—Deep muscle invasion 4—Through the entire bladder wall or with microscopic lymphatic invasion

Of the 34 recorded deaths, operation in twelve was for purely palliative reasons with no hope of cure Twenty one died of carcinoma, and thirteen died of other causes Although renal disease must have contributed in part to the fatal outcome in many cases, only four patients died from causes directly attributal to renal failure

Results as regards grade of tumor and depth of penetration are expressed in table 2

All cases are not included in this tabulation In a few cases, pathology reports were not complete In others, the bladder was not removed As one would expect, the deeper the penetration and the higher the grade of malignancy the shorter the period of survival

A similar tabulation on the survivors gives the following picture:

TABLE 3

Living†

	GRADE OF TUMOR (BRODERS' CLASSIFICATION)		
	Grade 2	Grade 3	Grade 4
Number	10	8	4
Average survival	44 months	27 months	21 months

*Depth of Penetration**†

	1 & 2	3	4
Number	14	1	7
Average survival	39 months	30 months	29 months

* 1 & 2—Mucosa and superficial muscle invasion. 3—Deep muscle invasion. 4—Through the entire bladder wall or with microscopic lymphatic invasion.

† No cases under twelve months included.

It is surprising to note that with advanced and presumably hopeless cases, we have an average survival period of between 2 and 3 years, with two in the 3–4 year group, and one in the 4–5 year group. Furthermore these patients are living in comparative comfort. When one compares the general appearance and outlook of these people with those in the end stages of vesical carcinoma treated by other means, he becomes convinced that these patients should be operated upon, even though the possibility of a cure is remote. In addition, as our technique of cystectomy improves, and with radical lymph node dissection added, it is fair to assume that over-all results will be better than those obtained in this series.

It is in the large group of grade 2 lesions that our greatest opportunity for advancement lies. Certainly all grade 1 lesions are readily amenable to transurethral resection or electrocoagulation. The outlook in grades 3 and 4 lesions with extensive bladder wall penetration is very poor regardless of the type of surgery adopted. However, most people agree that radical cystectomy with lymph node dissection, or in more advanced cases pelvic evisceration, offers the best hope of cure and certainly the best palliation in these individuals.

In considering when to perform cystectomy, it might be well to re-emphasize several well-known facts concerning the pathology of carcinoma of the urinary bladder. These are as follows: 1) multicentric foci of epithelial change throughout the bladder; 2) varying degrees of malignancy in the same tumor; and 3) changes in the degree of malignancy of bladder carcinoma under continuous observation. A typical case representing each of these points will be presented.

Melicow[3] recently analyzed a series of ten tumor-bearing bladders compared with a series of ten controls, and found in all of the tumor-bearing bladders foci of urothelial hyperplasia. A similar finding has been observed by our department of pathology as exemplified in the following case. This patient had recurrent papillary carcinoma grade 2 (fig. 1), which appeared to be recurring too rapidly to be controlled transurethrally. A total cystectomy and bilateral ureterosigmoidostomy were performed. The bladder mucosa showed multiple areas of epithelial change scattered through normal appearing mucosa (fig. 2). Although these lesions are not recognizable grossly, even on direct inspection of the bladder, each of them must be considered a potential carcinoma. Findings such as these cast considerable doubt on the efficacy of partial cystectomy or fulguration in the treatment of many bladder neoplasms.

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[3] Melicow, M. M.: Histological study of vesical urothelium intervening between gross neoplasms in total cystectomy. J. Urol., 68: 261–278, 1952.

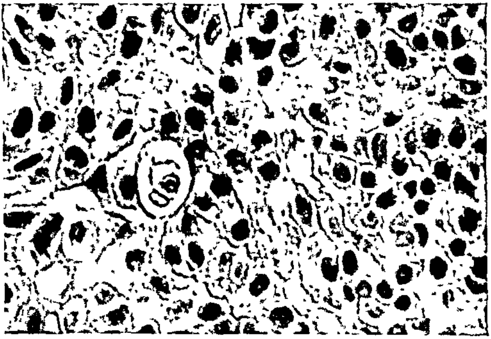
FIG. 1. Biopsy. Carcinoma grade 2. Cells fairly equal in size. Moderate mitotic activity.

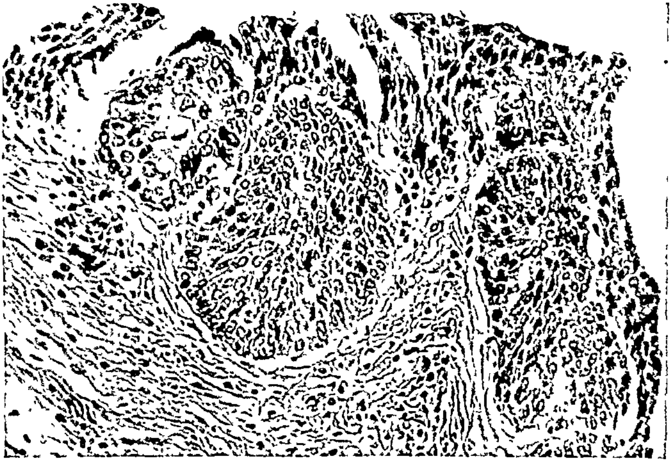
FIG. 2. Typical area of urothelial proliferation. Multiple areas, not visible on direct inspection, scattered over entire vesical mucosa.

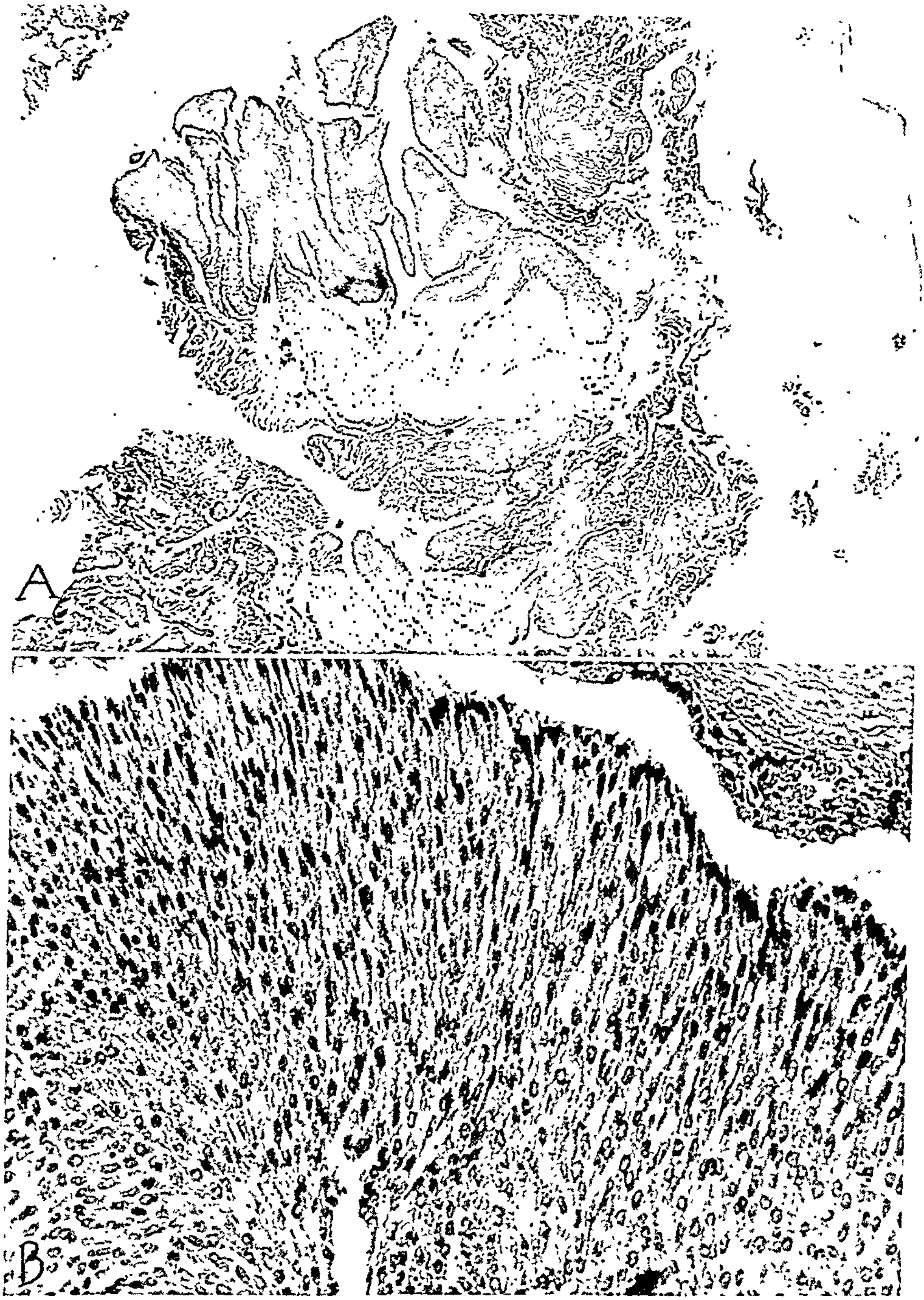

FIG. 3. *A*, transurethral biopsy. Diagnosis: Papillary carcinoma grade 1. *B*, high power section of A.

A second source of error is the presence of varying degrees of malignancy in the same tumor. Although generally recognized, this possibility is very frequently overlooked in evaluating biopsies taken transurethrally. It is emphasized by the accompanying case. This woman had a fair sized tumor of the left lateral wall and

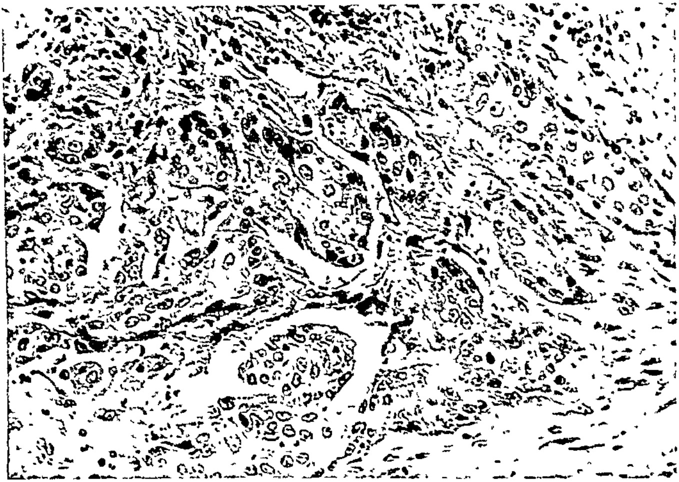

FIG. 4. Same tumor as figure 3. Note epidermoid appearance, high degree of malignancy compared to biopsy from same tumor.

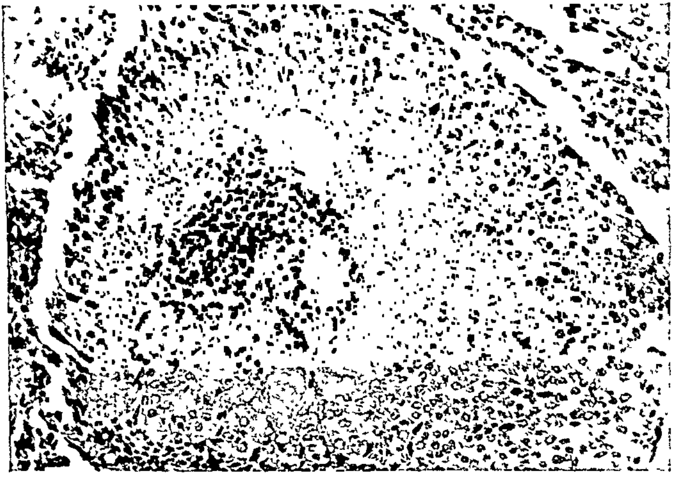

FIG. 5. Biopsy. Diagnosis: Papillary carcinoma grade 2. Specimen taken 1 year before that shown in figure 6.

floor of the urinary bladder. Initial sections were typical papillary carcinoma grade 1 (fig. 3). Deep bites were obtained with a resectoscope and at the time they were obtained, biopsies were considered adequate. Because considerable

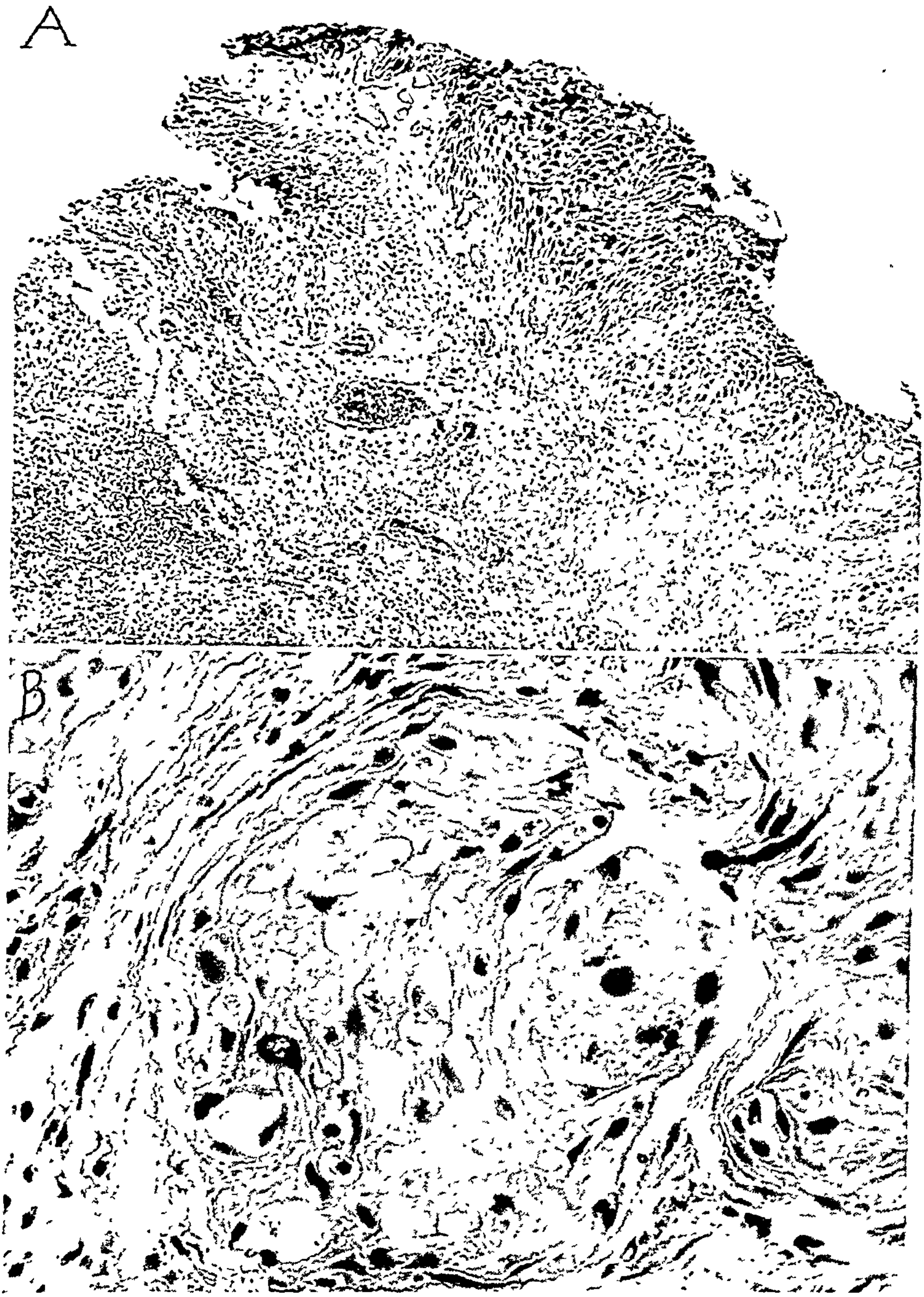

Fig. 6. *A*, biopsy, same tumor as that shown in figure 5. Still appears to be papillary carcinoma grade 2. *B*, same section as *A*. Note tumor cells in lymphatic channel. Prognosis very poor.

induration was felt through the vaginal wall, a total cystectomy was done and all grades of carcinoma were found in the tumor, including some areas which were epidermoid in character (fig. 4). If one had relied on the original biopsy alone in determining the method of treatment, he would most certainly have adopted the wrong procedure.

I am sure we have all had the unpleasant experience of following a relatively benign papillary carcinoma, grade 2, undergo several recurrences with the finding at a later date of an increased degree of malignancy and a comparatively hopeless prognosis Here is such a patient This 57 year old man was followed over a 3 year period, with hospital admissions at approximately one year intervals Earlier sections showed papillary carcinoma grade 2 (fig 5) On the third admission, a biopsy was taken which showed an increase of malignancy with the presence of tumor cells in the lymphatics, and a hopeless prognosis (fig 6)

The foregoing examples have not been presented because they are unusual I am sure every practicing urologist has experienced several similar situations They are presented, however, to emphasize the fact that we are dealing with a treacherous lesion and with one which is very likely to get beyond control with no warning whatsoever

SUMMARY

Results in a series of 69 cases of ureterosigmoid anastomosis for carcinoma of the urinary bladder, covering a 4½ year period, have been presented Three factors in the pathology of carcinoma of the urinary bladder were re emphasized, namely 1) multicentric foci of epithelial change throughout the bladder, 2) varying degrees of malignancy in the same tumor, and 3) changes in the degree of malignancy of bladder carcinoma under continuous observation The best hope for progress lies in a more accurate evaluation of the grade 2 papillary carcinomas, with earlier decision for cystectomy

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ESSENTIAL NOCTURNAL ENURESIS TREATED WITH d-AMPHETAMINE SULPHATE

SAMUEL I. ROLAND

From the Sub-Department of Urology, University of California School of Medicine, San Francisco, Calif.

That the treatment of essential nocturnal enuresis in children is not always successful is best shown by the multiplicity of drugs and devices in current use. Essential nocturnal enuresis is defined as urinary incontinence occurring during sleep in the absence of organic defects after the age of three.[1]

The association of enuresis with abnormally deep sleep has received little attention in the medical literature, although it is a frequent observation that most adults with enuresis give a history of heavy and sound sleep.[2, 3, 4] In our consecutive series of 51 children in whom there was no organic disease of the urinary tract or nervous system, a history of unusually deep sleep, with difficulty in awakening and the ability to sleep through marked noise and stimulation was found in 38 (74.5 per cent). All 51 children had urinary incontinence during the period of sleep, but only 4 were awakened by the stimulus of a wet bed.

RATIONALE FOR TREATMENT

The hypothalamus, primarily its lateral and possibly its posterior areas, is known to be associated with the mechanisms of micturition and sleep-waking. Kleitman[5] states that sleep is brought about by a break between the cortex and brain stem, probably in the hypothalamus. W. Russell Brain[6] considers normal sleep the result of interplay between the cortex and the hypothalamic sleep-waking center. Ranson, Kabat, and Magoun[7] found that stimulation of the hypothalamic region induces contraction of the bladder and others[8] have shown that bilateral cortical lesions produce signs of release of the bladder reflexes and an increase in the response to detrusor stretch. This is in keeping with Denny-Brown and Robertson's statement[9] that cortical control of the bladder consists of inhibition of spinal reflexes.

The action of the hypothalamic centers for micturition is dependent on the intact motor cortex fibers descending through the internal capsule.[10] It is well

Accepted for publication February 27, 1953.

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known that subcortical lesions in the frontal region may cause both incontinence and excessive sleep, as distinct from coma[11] After the operation of prefrontal leucotomy, the combination of drowsiness, deep sleep, and urinary incontinence during the first week or two is common[2]

While our knowledge of the mechanism of micturition is incomplete, there seems to be an anatomic functional relationship between deep sleep and urinary incontinence Consequently, a clinical study was undertaken to see if enuresis could be blocked by the sleep-opposing action of amphetamine

MATERIALS AND METHODS

A consecutive series of 51 patients were screened by physical examination, urinalysis, sacral x rays if indicated, and by cystoscopic studies in children suspected of having organic urological difficulty In none of these patients was any organic illness or deformity found, they all fitted in the category commonly called psychogenic or essential nocturnal enuresis The ages ranged from 4 to 12 years There were 30 female and 21 male patients Thirty eight children (74 5 per cent) had a history of unusually deep or prolonged sleep All were given 5 mg of d amphetamine sulphate in an elixir, at bedtime, for one week They were requested to void before going to bed, and were instructed to turn off an alarm clock that had been set to ring 4 hours later The child was told to arise, turn off the alarm, void, and return to bed At no time was the parent to assist the child in turning off the alarm or to guide the child to the toilet If the treatment was unsuccessful after 1 week at the 5 mg dose, it was raised to 10 mg and the same awakening routine was used If two dry nights occurred in the first week, the smaller dosage was continued for 3 weeks and then stopped Even if enuresis ceased, the routine was continued for 21 days If enuresis persisted after the 10 mg dosage for 2 weeks, the treatment was discontinued A dosage of 15 mg was tried, but in our experience it was of no value if the 10 mg quantity had been proved unsuccessful No toxic or untoward reactions were reported, nor was sleeplessness, unusual restlessness or alertness noted during the period of therapy

RESULTS

Forty seven out of 51 cases, or 92 per cent of the cases treated, were relieved of enuresis within three weeks and remained dry at night with only rare incontinence for at least six months thereafter, the period for which all cases were followed Thirty nine of the patients were dry within a week after beginning the 5 mg dosage and seven of these responded immediately after the initial dosage, but most cases required from three to five nights of treatment before enuresis was interrupted In the remaining 8 cases in which improvement was observed, it was necessary to give 10 mg after treatment for 7 days with the smaller dosage had failed In the remaining 4 cases no results were obtained even after one month's re trial following a month without therapy One case was retreated in 30 days and did well after 4 doses of 10 mg of d amphetamine sulphate on 4 successive nights and has remained continent for the past 14 months. The patients who were counted as successfully treated had an occasional incontinent night, but none had more than 8 incontinent nights in 6 months, with more than half of them completely relieved of their nocturnal enuresis with no subsequent incontinent nights.

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[11] Michaels J and Rudoy, M Use of ephedrine sulfate in control of enuresis in schizo phrenic regression J Nerv & Ment Dis , 111 147-153, 1950

DISCUSSION

The results from the method described have been compared with those of other methods of therapy of essential nocturnal enuresis reported in the past 30 years. Statistically, our method appears to have given better results than any previously described. It has been compared with the use of ephedrine,[11, 12] D-desoxyephedrine,[13] atropine,[14] chorionic gonadotropin,[15] thyroid extract,[16] testosterone,[17] other endocrine therapy,[18] an epiphyseal preparation,[19] pervitin,[3] and various mechanical devices.[20, 21] The treatment with amphetamine sulphate has a rational physiologic basis, is inexpensive, lacks toxicity or hazard, and can be recommended for the treatment of this common and difficult problem.

SUMMARY AND CONCLUSIONS

Of 51 children with essential nocturnal enuresis, 38 (74.5 per cent) gave a history of excessively heavy and prolonged sleep.

Ninety-two per cent of all patients responded effectively to d-amphetamine sulphate given as described. In some, increased dosage gave a prompt response when a lesser amount was unsuccessful.

No untoward reaction to d-amphetamine sulphate was observed. It appeared that the tolerance to this drug was greater than normal in these patients.

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EFFECT OF CORTISONE ON PATIENTS WITH CARCINOMA OF PROSTATE

WILLIAM L VALK and ROBERT H OWENS

From the Department of Urology University of Kansas Medical Center, Kansas City 12, Kansas

The hormonal inhibition of carcinoma of the prostate has been observed clinically and statistically now for 11 years and there is general agreement that bilateral orchiectomy and estrogen therapy will greatly improve the 5-year survival of these patients, but that the mortality after 5 years in the treated and untreated series is identical, both being about 85 per cent [1]

Since the reticular zone of the adrenal cortex produces steroids similar to the gonadal androgens and estrogens, changes in this organ stimulated by treatment, namely orchiectomy and estrogen therapy, have been held responsible for the reactivation of the neoplasm [2] It is well known that hyperplasia of the adrenal cortex occurs after orchiectomy and also after estrogen treatment [3] In an effort to control this new source of androgen Huggins and Scott did bilateral adrenalectomy on 3 patients with relapsing carcinoma of the prostate in 1945 with rather indifferent results because of the difficulty of adrenal replacement at that time [4] In 1951 cortisone made possible adequate adrenal-cortical replacement and a larger series of bilateral adrenalectomies has now been carried out for patients with relapsing carcinoma of the prostate, for patients with metastatic carcinoma of the breast, and for patients with hypertension Approximately 50 per cent of the relapsing carcinomas of the prostate have been benefited by this additional procedure [5] Obviously, this progressive surgical endocrine elimination is not an ideal treatment of carcinoma of the prostate and certainly should not be considered a specific therapy since the whole endocrine relationship in carcinoma of the prostate is but poorly understood Adrenalectomy is, however, an extremely valuable research technique in improving our understanding of the hormonal dependency of neoplasms and it has been carried out on patients with relapsing carcinoma of the prostate and metastatic carcinoma of the breast at the University of Kansas Medical Center

Figure 1 represents our conception of the interaction of the various endocrine groups involved in carcinoma of the prostate Albright et al [6] suggested such a system of interaction We have enlarged on their ideas and created a hypothesis

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Read at annual meeting South Central Section American Urological Association Hot Springs Ark September 30 1952

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[4] Huggins, C and Scott W W Bilateral adrenalectomy in prostatic cancer Ann Surg 122 1031-1041 1945

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of cyclical response in the male. If this hypothesis is correct, we can understand what occurs in carcinoma of the prostate after various endocrine approaches. It is important that luteinizing hormone will stimulate both the Leydig cells of the testicle and the cells of the reticular zone of the adrenal cortex.[6] This being true, following orchiectomy, only the cells of the adrenal cortex are left to respond to luteinizing hormone stimulation. The response in estrogen therapy is due to the suppression of follicle stimulating hormone; however, estrogen may stimulate luteinizing hormone. Thus, after orchiectomy and estrogen therapy the luteinizing hormone remains uninhibited and could eventually stimulate the adrenal cortex into hyperplasia with increased androgen secretion and relapse in the carcinoma. It is evident, therefore, that orchiectomy and estrogen therapy, although efficacious, do not entirely remove all carcinoma-stimulating androgen. When given over a long period of time, estrogen may even cause relapse by stimulating adrenal cortical hyperplasia.

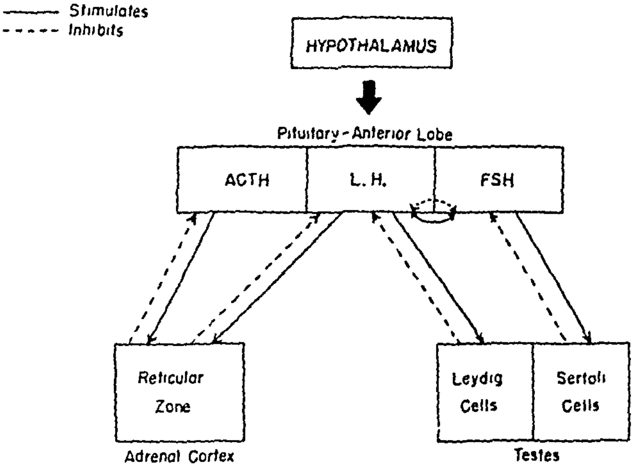

FIG. 1

There is some evidence that cortisone will suppress the luteinizing hormone.[7, 8, 10] Wilkins, et al. have shown that as little as 25 mg. per day of cortisone would suppress excessive androgen in adrenocortical hyperplasia.[9] It is now known that atrophy of the adrenal cortex may occur after prolonged or excessive use of cortisone with adrenal insufficiency and death.[11, 12] It has been our specific aim to produce adrenal cortical insufficiency with large doses of cortisone in patients with disseminated carcinoma of the prostate with the hope that therapy might be evolved or at least a preliminary clinical test useful in predicting which

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[7] Antopol, W., Glaubach, S. and Quittner, H.: Rheumatism, **7**: 187–196, 1951.

[8] Brokow, R., Briseno-Castrijon, B. and Finerty, J. C.: Texas Repts. Biol. Med., **8**: 312–319, 1950.

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[10] Selye, H.: Annual review of stress. Acta, Montreal, 1951.

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[12] Fraser, C. G., Preuss, F. S. and Bigford, W. D.: Adrenal atrophy and irreversible shock associated with cortisone therapy. J.A.M.A., **149**: 1542–1543, 1952.

patients with carcinoma of the prostate might be benefited by surgical adrenalectomy. With a combination of cortisone and estrogen not only would the adrenal gland be inhibited, but to a considerable degree the pituitary would be suppressed. It would appear from figure 1 that cortisone would suppress ACTH and the luteinizing hormone, and estrogen the follicle stimulating hormone. Cortisone alone may have some direct depressive effect on the neoplastic cell (either through direct action on the cell or by suppressing the somatotropic hormone of the anterior pituitary). Four patients with widespread carcinoma of the prostate were treated with various combinations of the above agents.

CASE REPORTS

Case 1. A. T., 52-1363, a 72 year old colored man (fig. 2) had been admitted with a 2-year history of prostatism, severe bone pain requiring daily opiates, and urinary retention. Physical examination revealed a chronically ill, poorly nourished man with severe pain in back, pelvis, chest, and thighs. The prostate was 3 plus carcinomatous with infiltration into the seminal vesicles and base of the bladder. X-rays of chest, spine, pelvis, and thighs showed extensive osteoblastic metastases typical of carcinoma of the prostate. Laboratory studies: hemoglobin 33 per cent, acid phosphatase 3.79 millimoles, and alkaline phosphatase 24.8 millimoles. In order to observe the effect of cortisone alone on carcinoma of the prostate, this patient received 300 mg. per day for 60 days. After one week, pain and discomfort had lessened at least 50 per cent and at the end of the second week the patient was entirely free of pain and has continued so to the present. Paralleling the clinical improvement there was a marked drop in the acid phosphatase from 3.79 to 1.5 millimoles in 30 days. Dosage of cortisone was then dropped to 100 mg. a day for 30 days and eventually continued to the present at 25 mg. per day. Bilateral orchiectomy was carried out at 60 days and stilbestrol 5 mg. a day was started after the third month because we felt that the combination of these

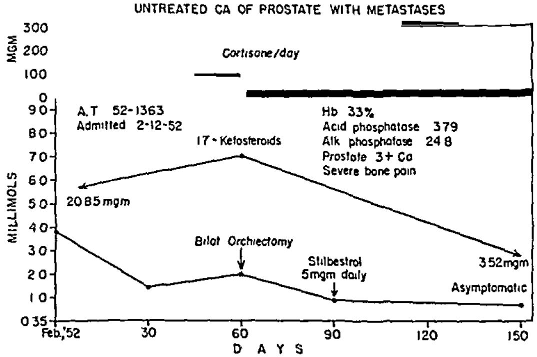

FIG. 2

of cyclical response in the male. If this hypothesis is correct, we can understand what occurs in carcinoma of the prostate after various endocrine approaches. It is important that luteinizing hormone will stimulate both the Leydig cells of the testicle and the cells of the reticular zone of the adrenal cortex.[6] This being true, following orchiectomy, only the cells of the adrenal cortex are left to respond to luteinizing hormone stimulation. The response in estrogen therapy is due to the suppression of follicle stimulating hormone; however, estrogen may stimulate luteinizing hormone. Thus, after orchiectomy and estrogen therapy the luteinizing hormone remains uninhibited and could eventually stimulate the adrenal cortex into hyperplasia with increased androgen secretion and relapse in the carcinoma. It is evident, therefore, that orchiectomy and estrogen therapy, although efficacious, do not entirely remove all carcinoma-stimulating androgen. When given over a long period of time, estrogen may even cause relapse by stimulating adrenal cortical hyperplasia.

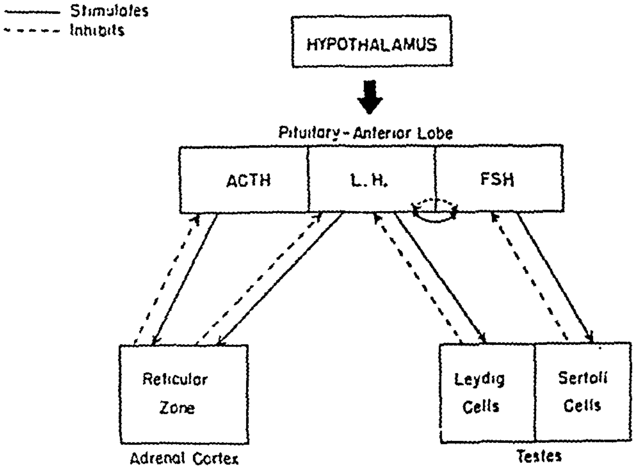

Fig. 1

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[7] Antopol, W., Glaubach, S. and Quittner, H.: Rheumatism, 7: 187–196, 1951.

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[12] Fraser, C. G., Preuss, F. S. and Bigford, W. D.: Adrenal atrophy and irreversible shock associated with cortisone therapy. J.A.M.A., 149: 1542–1543, 1952.

phatase was 11 6 millimoles X-ray examination showed involvement of nearly all of the skeleton with typical osteoblastic areas This patient was dismissed on 5 mg of stilbestrol a day and was asymptomatic for a period of 5 months when the *pain in his hips and legs recurred By October 1951 the pain was* severe enough to be disabling and x ray examination showed extension of the previously noted osteoblastic metastases The prostate was small but very hard and irregular The serum acid phosphatase was elevated and in December 1951 he was started on cortisone 300 mg a day which was reduced to 200 mg a day after 6 days of treatment and then after 1 week this was reduced to 100 mg when it was noted that the patient had considerable relief from pain This improvement continued through January 1952 and he was then discharged home on 100 mg of cortisone a day and 5 mg a day of stilbestrol After 6 weeks there was recurrence of pain and the patient again was obviously out of control He was continued on 100 mg of cortisone daily until May 1952 when he discontinued the cortisone and was re admitted to the hospital in extremis exhibiting typical signs of adrenal cortical insufficiency In spite of vigorous efforts he died 2 weeks after admission to the hospital It is interesting to note that the 24 hour 17-ketosteroid excretion the last week before death was nil, indicating good suppression of androgen output and also exhibiting good evidence of total hormonal independence of this undifferentiated carcinoma

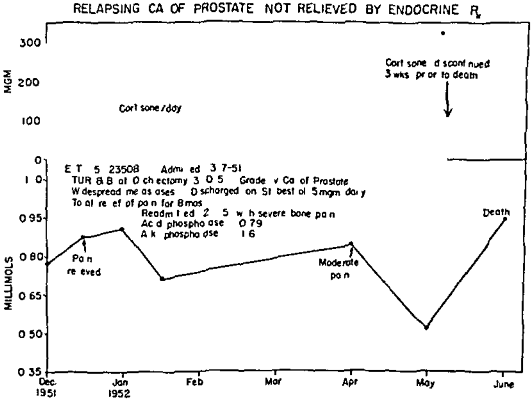

FIG 4

Case 4 R N , 50 4779, a 67 year old white man (fig 5) was admitted to the hospital on July 3, 1950 with urinary retention and an enlarged, infiltrating, fixed carcinomatous prostate X ray evidence of bony metastases was present and the serum acid phosphatase was elevated on admission Transurethral resection of the prostate and bilateral orchiectomy were carried out and the patient was dismissed on 5 mg of stilbestrol a day He obtained complete relief for 1 year and then had a recurrence of all of his former severe pain In October 1951 he was readmitted to the hospital and at that time there was x-ray evidence of progression of the metastatic areas in the skeleton and the acid phosphatase was 5.6 millimoles. He was started on cortisone 300 mg. a day for 48 hours and then 200 mg. a day for 48 hours and then 100 mg. a day for one month. On the sixth day of cortisone therapy this patient had complete relief of pain, increased appetite and sense of well-being, and a serum phosphatase reduced from 5.6 to 1.6 millimoles per liter. During the second month of therapy cortisone was reduced to 50 mg. per day and there was almost immediate recurrence of pain and marked increase of the serum acid phosphatase to 11.1 millimoles. Cortisone was increased, first to 100 mg. a day with relief of pain and then to 300 mg. a day for 30 days and the phosphatase continued to drop until it reached a level of 1.0 millimoles. In August 1952 this patient stopped taking cortisone; and 2 weeks after stopping this drug pneumonia developed and the patient died. This patient demonstrates the effect of cortisone on the metabolism of the cancer cell causing a decrease in the production of acid phosphatase and of control of the neoplasm by a combination of orchiectomy, estrogen, and cortisone.

RELAPSING CA OF PROSTATE WITH METASTASES

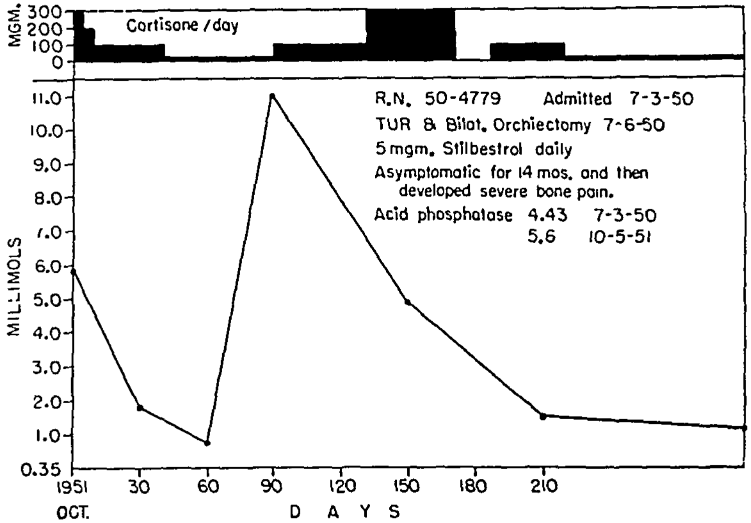

FIG. 5

DISCUSSION

Four additional patients with relapsing carcinoma of the prostate are now under treatment and appear to have a desirable palliation from this therapy. Since euphoria and even decreased pain have been reported by many persons using cortisone in large dosages these clinical findings would mean little unless strengthened by definite chemical evidence of regression of the neoplasm as evidenced by decrease in acid phosphatase. As this has occurred in six of the 8 patients we feel that the cortisone in producing medical adrenalectomy has a definite inhibiting effect on the neoplasm. A comparison of the roentgenological studies taken before and after cortisone treatment has failed to show any marked improvement in the metastatic areas Inasmuch as the longest case has been studied only 9 months, this is not unusual since even in the most favorable carcinomas treated by orchiectomy there is seldom x-ray change under one year Although we have followed the 17-ketosteroid excretion in each of these patients before, during, and after treatment, this laboratory study likewise is of little value since the cortisone itself is broken down into 17-ketosteroid degeneration products

Many undesirable effects from cortisone therapy have been observed in our patients It has been difficult to control the Na retention and edema by merely a salt-poor diet in some patients so that NH_4Cl and Hg diuretics were necessary Depletion of the cellular and serum K has required careful replacement with 2–3 grams of KCl orally daily One patient developed a recurrence of an old peptic ulcer while on cortisone Since the HCl output is greatly stimulated by cortisone and ACTH, all of the patients were prophylactically given antacids Close watch of the blood sugar level is necessary in all patients receiving cortisone Since August 1, 1952 Merck and Company have generously supplied us with adequate amounts of cortisone to continue this study another year Euphoria in these patients has not been considered an undesirable effect

CONCLUSION

Inhibition of the pituitary and adrenal cortex appears feasible by the use of cortisone and estrogen

From the theoretical side and from the evidence presented by this small and inadequate series, it appears that bilateral orchiectomy, estrogen, and cortisone will give maximal inhibition of far advanced carcinoma of the prostate

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RUPTURE (FRACTURE) OF THE PENIS

ROBERT F. THOMPSON

Rupture of the penis is a rare condition. Some urological textbooks refer to it in brief fashion, while others fail to mention the subject. In 25 years of medical practice only one instance of this condition has been encountered (the case to be reported) and at four recent urological meetings inquiry failed to find a urologist who had ever seen a case in his practice. During undergraduate days, our professor of urology described a case which he had treated in private practice, but it was never recorded.

Considerable correspondence and an untiring effort on the part of the research staff of a medical reference library was necessary before the few cases on record could be located. There is no instance of this condition in the records of the four local hospitals. Fetter and Gartman studied the literature in 1936 and found only ten reported instances of rupture of the penis in the previous decade. Excluding war injuries, no additional cases have been found on record.

ETIOLOGY

The injury is produced either by direct blow upon the surface of the penis or from the bending of the erect organ. The penis must be erect for the accident to occur. The injury is usually produced as follows:

1) By accident during coitus –*faux pas de coit.*

2) By injury to the erect penis due to contact with a hard object, such as may be caused by sudden movements of the body or hand, either while the patient is asleep or awake, by a) rolling over in bed, b) striking organ against toilet seat, c) bumping into furniture in the dark, d) catapulted against dash board of suddenly stopped automobile, e) caught in sleeping garment or bedding and f) mashed or kicked by animal.

3) By "breaking a chordee" to relieve the pain of a gonorrheal erection.

PATHOLOGY

The lesion consists of a tear of the fibrous sheath of the corpora cavernosa. Each corpora is protected by a fibrous layer, the tunica albuginea, which during erection becomes thinned out, and is susceptible to injury and rupture when trauma occurs. Hemorrhage, with the formation of a hematoma, now occurs, and the severity of the accident depends upon the extent of the tear and the size of the resulting clot formation. If the urethra is torn, the severity of the situation is greatly aggravated.

The organ now becomes markedly swollen and discolored. The swelling and bluish ecchymoses may extend to the scrotum and perineum and even over the thighs and upon the abdomen. The penis now bends toward the uninjured side in a bizarre fashion.

The penis must be in the erect state for this injury to occur. If it is traumatized

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Read at annual meeting, South Central Section, American Urological Association, Hot Springs, Ark., October 1, 1952.

in the flaccid state, usually nothing more serious than a subcutaneous ecchymosis is likely to result

SYMPTOMS AND DIAGNOSIS

Following the accident, the pain is severe, often causing the victim to faint from the shocking sensation which is present He may recall hearing a definite sharp, cracking sound preceding the collapse of the erection and the onset of pain and shock The sound has been described as resembling the breaking of a glass rod The event resembles to a certain extent the fracture of a bone Immediately following, there is marked swelling and deformity of the organ Urination may be difficult or impossible depending upon the extent of the injury and the size and pressure of the hematoma Blood will flow from the meatus if the urethra has been torn

The patient may not seek medical aid for a period of time being loath to disclose his condition and the events leading up to the accident However, marked swelling and deformity and pain will finally send him to a physician The diagnosis is not difficult The history may be vague yet from the appearance of the patient, in pain, and with a deformed, distorted organ it is usually evident that a rupture has taken place and that the injury is not a simple contusion

TREATMENT

Conservatism is the watchword concerning the care of these cases This is the opinion of all the authors who have encountered such accidents A Foley catheter should be inserted and a snug, compress dressing applied with an encircling bandage making counter pressure against the catheter This may check further bleeding Later, it may be necessary to evacuate the hematoma by incision Any active bleeding vessels can be ligated

In severe cases where the urethra is lacerated and it is impossible to pass a catheter from the meatus upward, cystotomy can be performed and a catheter placed in the channel by retrograde catheterization Or diversion of the urinary stream can be done until the torn urethra has healed

PROGNOSIS

The prognosis should be guarded Depending upon the extent of the injury and the amount of damage to the urethra and corpora bodies, a certain amount of erectile difficulty may result with distressing bending of the erect organ The patient must be warned against these possible, unfortunate developments

CASE REPORT

A ranch hand, aged 38, was brought to the hospital in great pain, with a markedly, swollen, distorted penis Opiates were necessary for relief

Examination revealed the entire penis to be markedly swollen and distorted by a large fluctuant hematoma (fig 1) The mass was firm in the upper portion, but most of it was of soft consistency

The history was vague and difficult to obtain He worked on a ranch and the injury had occurred in the corral It was impossible to get the exact details leading up to the injury. His family was of the opinion that he had been kicked by one of the horses in the corral.

No bleeding had occurred from the urethra and the patient was able to urinate satisfactorily. A Foley catheter was introduced successfully and a compress dressing was encircled about it thereby controlling the bleeding which was still taking place into the corpora bodies.

Ten days later after all active bleeding had ceased, an incision was made over the fluctuant area and an enormous amount of clots were evacuated. A drain was inserted and another compress dressing was applied about the Foley catheter which was in place.

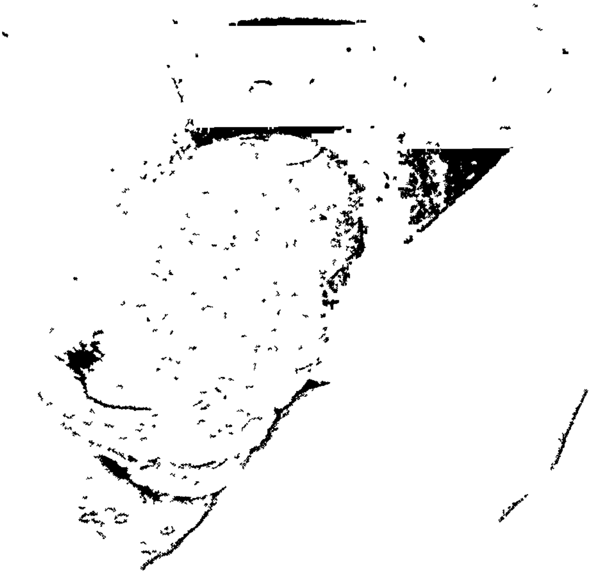

FIG. 1. Convex angulation and deformity of fractured penis

Healing was very rapid and in a week's time all of the swelling had subsided. He left the hospital 6 days after the operation. He visited the office twice after leaving the hospital but failed to remain under observation as advised. He was urinating satisfactorily. There was considerable pain and marked deformity on erection, he stated.

A year and a half later his employer reported that the patient was working regularly and had no complaint.

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CLINICAL VALUE OF UREA CLEARANCE AND PHENOLSULFONPHTHALEIN TEST

A. D. MITCHELL, ROBERT OWENS AND W. L. VALK

From the University of Kansas School of Medicine, Department of Surgery, Section of Urology, Kansas City 12, Kansas

To think intelligently about renal function, the per cent of normal function present in the vascular, glomerular and tubular segments of the functioning nephron should be known.[1]

In this paper we determine how accurate a percentage estimate of renal function can be made from these tests, phenolsulfonphthalein and urea clearance, comparing them to clearance and tubular mass studies. These latter studies have the advantages of accurately timed catheter urine collection, duplicate plasma samples at the beginning and end of urine collection periods, and a stable blood level of test substances maintained by constant infusion.

To make these comparisons have practical significance, urea clearance and phenolsulfonphthalein tests were carried out by the routine ward manual procedure. Thus, any errors of bladder emptying or of inaccurate timing on the part of ward personnel have not been corrected.

In this study we accept as valid standards of reference, clearance of inulin as glomerular filtration rate, clearance of sodium p-aminohippurate as effective renal plasma flow (EPF) and PAH TM as maximum excretory tubular function.

GLOMERULAR FILTRATION RATE

Inulin is quantitatively filtered by the glomerulus and is neither excreted nor reabsorbed by the renal tubule. Urea is filtered by the glomerulus but passively diffuses through the tubular epithelium in variable quantities depending on the rate of urine formation. With less urine formation more glomerular filtrate is reabsorbed and more urea diffuses out of the filtrate. For urine flows of 2 cc/min or more, urea clearance $= UV \div B$ and 75 cc/min is the accepted normal value. This is referred to as the maximum urea clearance. For urine flows under 2 cc/min, urea clearance $= U\sqrt{V} \div B^*$ and 54 cc/min is the accepted normal value. This is referred to as standard urea clearance. (U = Urine concentration of urea. V = Urine flow in cc/min. B = Blood urea.)

In figure 1, *A* standard urea and inulin clearances are compared for 33 patients. In 24 of these patients C_U was below C_{IN}. Correlation as to per cent of normal was fairly valid in only ⅓ of the patients. In figure 1, *B* the same results are plotted with 40 cc/min as normal for standard urea clearance. Urea clearance is

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Read at annual meeting, South Central Section, American Urological Association, Hot Springs, Ark., September 30, 1952.

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[1] Valk, W. L. and Mitchell, A. D.: Segmental renal function studies. J. Urol., 64: 254, 1950.

* Smith[2] has pointed out that this is by definition not a true clearance.

[2] Smith, H. W.: The Kidney, Structure and Function in Health and Disease. New York: Oxford University Press, 1951, p. 66.

above C_{IN} 17 times and below 16 times. Valid correlation is no higher than in figure 1, *A*.

In figure 2, *A* maximum urea and inulin clearances are compared for 44 patients. In 36 of these patients C_U was below C_{IN} and in only 11 was correlation valid. By changing the normal value of C_U to 60 cc/min in figure 2, *B* C_U is below C_{IN} 23 times, above 12 times, and nearly the same in 9 patients. Again, however, there are only about ¼ that correlate well.

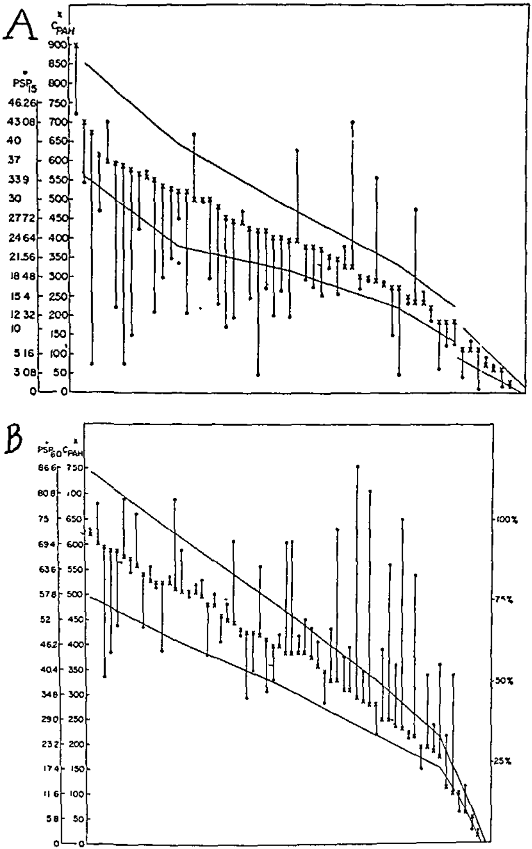

FIG. 1. *A*, Comparison of standard urea clearance (dot) and inulin clearance (x) at accepted normal values in 33 patients. Not determined simultaneously. *B*, comparison of standard urea clearance (dot) and inulin clearance (x) using 40 cc/min. urea clearance as normal. Same patients as in *A*.

To determine how much difference in C_U and C_{IN} was due to errors in ward

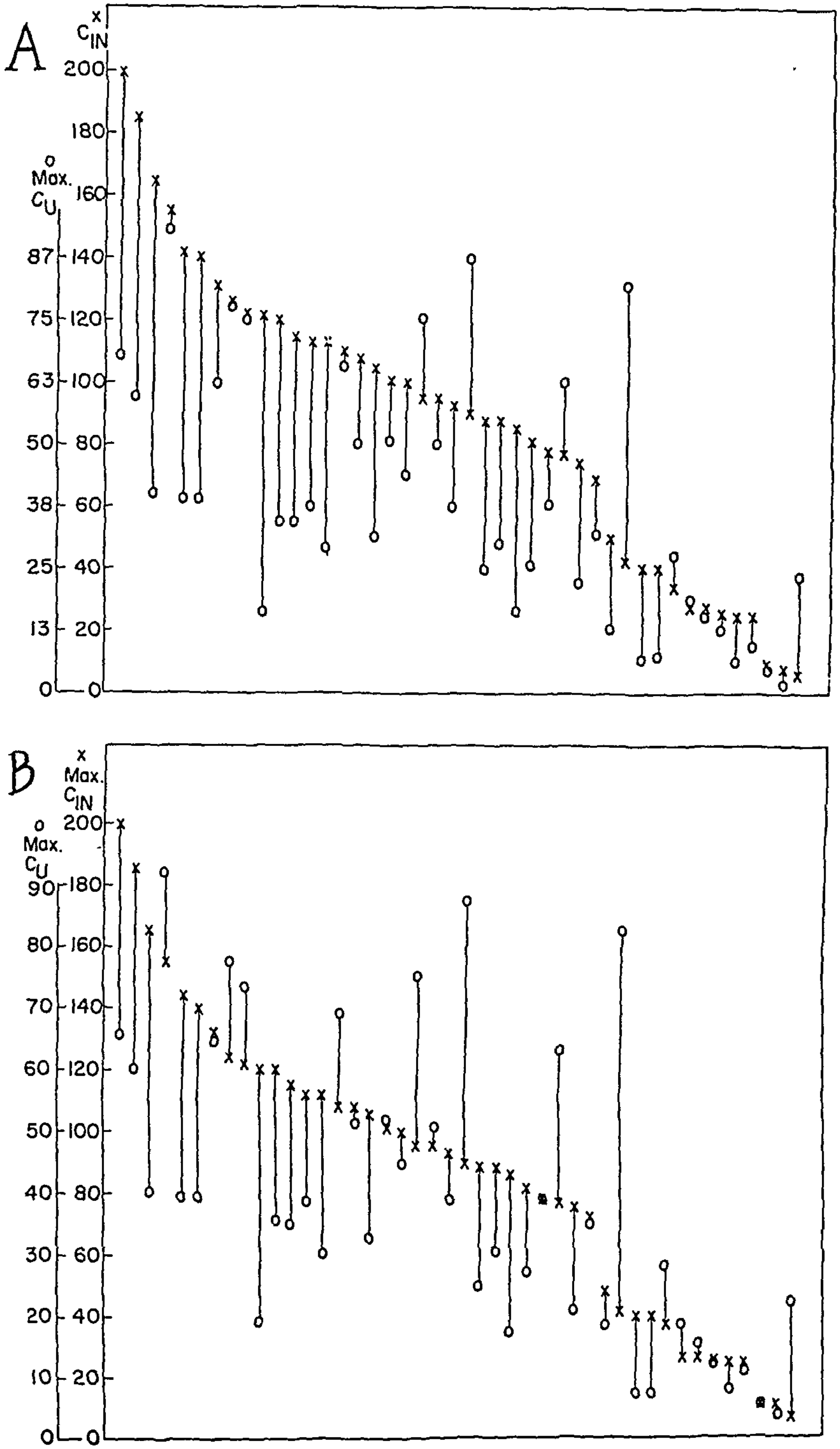

FIG. 2. *A*, comparison of maximum urea clearance (circle) and inulin clearance (x) at accepted values in 44 patients. *B*, comparison of maximum urea clearance (circle) and inulin clearance (x) using 60 cc/min. clearance as normal. Same patients as in *A*.

technique 38 simultaneous inulin and urea clearances were done. Figure 3 shows that in these 38 patients C_U was below C_{IN} in 20 instances and above C_{IN} 18 times. There were 15 valid correlations.

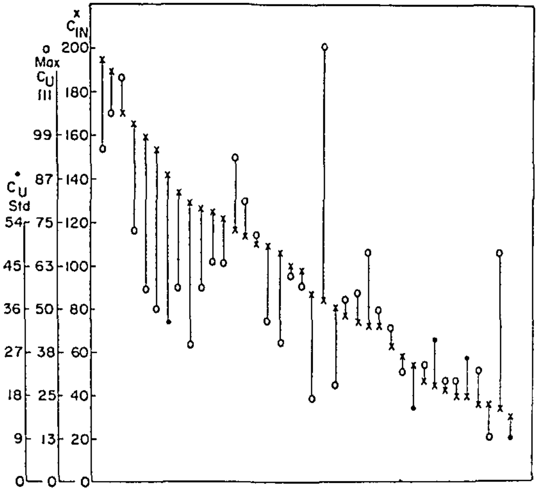

FIG. 3. Comparison of simultaneous urea clearance and inulin clearance in 38 patients using accepted normal values. Maximum urea clearance (circle), standard urea clearance (dot), inulin clearance (x).

TUBULAR FUNCTION

Valid measurement of maximal tubular excretory function is obtained by determining Diodrast or sodium para-aminohippurate TM.[3] [4] Since PSP is almost entirely excreted by tubular function, comparison of 15 and 60 minute excretion of PSP with PAH TM was made in 43 patients. No interpretable results were obtained. This was expected since the intravenous injection of 6 mg of PSP does not approach a TM level of this dye.

EFFECTIVE RENAL PLASMA FLOW

The clearance of PAH at low plasma levels is a measure of effective renal plasma flow and the true clearance of PSP, not to be confused with the PSP test under discussion, is also a measure of this function, although the average clearance is only about 60 per cent of PAH clearance. PSP and PAH are transported across the tubular epithelium by the same enzyme system.[3] After the injection of 6 mg. of PSP intravenously, as in the routine PSP test, the plasma level should not exceed 0.25 mg. per cent in the average adult and would therefore be below the clearance level concentration.

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[3] Smith, H. W., Goldring, Wm. and Chasis, H. Measurement of tubular excretory mass, effective renal blood flow, and glomerular filtration rate in the normal human kidney. J. Clin. Invest., 17: 263, 1938.

[4] Chasis, H., Redish, J., Goldring, Wm., Ranges, H. A. and Smith, H. W.: The use of sodium p-aminohippurate for the functional evaluation of the human kidney. J. Clin. Invest., 24: 483, 1945.

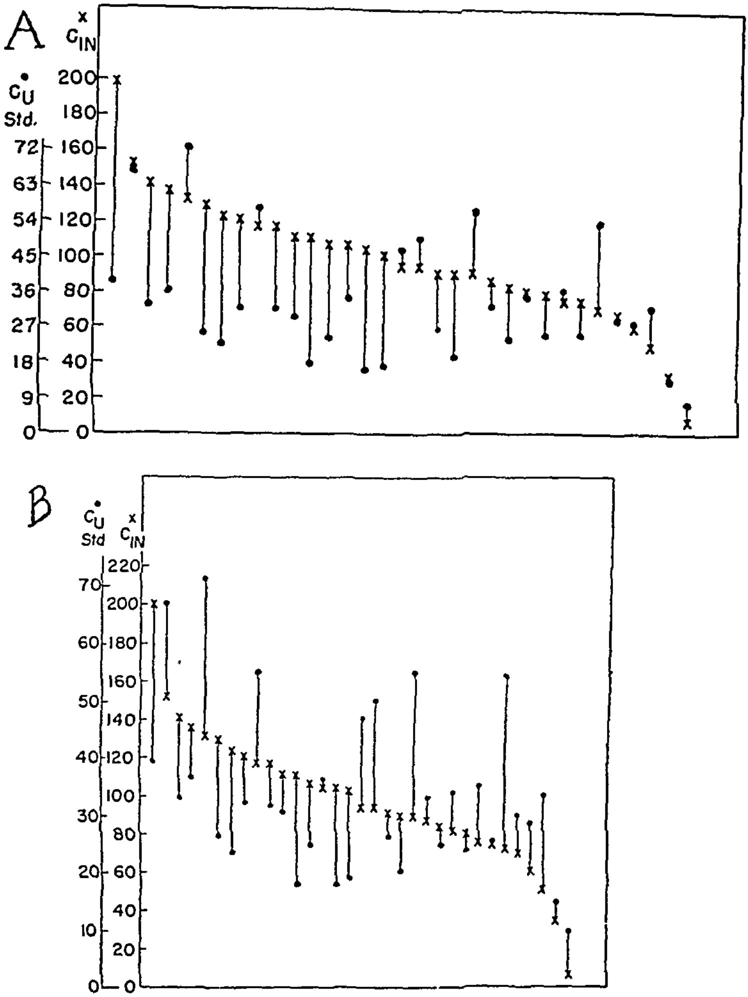

FIG. 4. *A*, comparison of the per cent excretion of 6 mg. PSP (dot) in first 15 minutes after intravenous injection with clearance of PAH (x) using accepted values in 56 patients. Left hand columns: PSP in per cent of injected dye and PAH clearance (C_{PAH}) in cc/min. Area enclosed by diagonal lines is 20 per cent above and below C_{PAH}. *B*, comparison of per cent excretion of 6 mg. PSP (dot) in first 60 minutes after intravenous injection with clearance of PAH (x) using accepted values in 61 patients. Left hand columns: PSP in per cent of injected dye and PAH clearance (C_{PAH}) in cc/min. Right hand column: Per cent of normal PAH clearance. Area enclosed by diagonal lines is 20 per cent above and below C_{PAH}.

In view of these facts it was thought that some correlation between PAH clearance and PSP excretion might exist. In comparing these results, PAH clearance was not corrected to a standard surface area since PSP results are not so corrected. All results were included even though some seemed impossible to justify. It is usually accepted that the average adult should excrete 40–42 per cent of the 6 mg. of intravenously injected PSP in the first 15 minutes and a total of 75 per cent in the first hour. A shift of maximal excretion to the later periods indicates impaired function.

Comparison of the 15 minute excretion of PSP with PAH clearance in 56 patients (fig. 4, *A*) shows that only 17 correlate within 20 per cent either above or below the value for C_{PAH}.

Comparing the 60 minute excretion of PSP with PAH clearance in 61 patients (fig. 4, *B*) shows that 31 are within a zone of 20 per cent above or below the PAH clearance. PAH clearance was above 75 per cent of normal in 20 patients and 15 correlated in this zone. Between 75 and 50 per cent of normal PAH clearance there were 19 patients and 10 correlated in the 20 per cent zone. Below 50 per cent of normal PAH clearance there were 22 patients and only 6 correlated in this zone. The per cent of PSP excreted was above the corresponding level of PAH clearance in 65 per cent of the patients. Although a fairly consistent decrease in PAH clearance was present in this group of patients, ranging from 100 per cent to 5 per cent of normal, the per cent of PSP excreted in one hour was in excess of 35 per cent of the injected dye in 50 patients.

TABLE 1. C_{PAH} = *PAH clearance or effective renal plasma flow in cc/min*
C_{IN} = *inulin clearance or glomerular filtration rate in cc/min.*
TM_{PAH} = maximum tubular excretory capacity for PAH in mg/min. TM_G = minimum tubular reabsorptive capacity for glucose in mg/min. PSP_{15} = per cent excretion of intravenously injected 6 mg PSP in first 15 minutes. PSP_{60} = same value for 60 minutes

	C_{PAH}	C_{IN}	TM_{PAH}	TM_G	PSP_{15}	PSP_{60}
Nov. 1948	430	90	55	310	15	48
July 1949	277	62	33	287	18	40
Oct. 1949	416	79	30	190	17	40
May 1950	15	8		28		

Comparison of excretion of PAH and PSP simultaneously cannot be made since these substances compete with each other for excretion.

DISCUSSION

It is indeed disappointing that such poor correlation of C_U and C_{IN} was obtained, but not surprising, since Chasis and Smith[5] obtained a urea/inulin clearance ratio ranging from 0.35 to 0.68 in 10 normal subjects.

Lowering the so-called normal values for standard and maximum urea clearance did not improve the degree of correlation in our patients. Simultaneous urea and inulin clearances were about equal as to urea clearance being above or below inulin clearance and correlation was improved showing that errors of collection and timing contribute to part of the error in the ward clearances.

In discussing the clinical use of urea clearance, Smith[2] states, "The more exact interpretation of the pathological physiology of the kidney cannot rest upon the assumption that the urea clearance bears any constant relationship to the filtration rate, for urea is too diffusible and its excretion involves too many variables as judged by the inulin clearance. . . . But the fact remains that, for ease and rapidity in assessing renal function in general ward service, the urea clearance is unequalled."

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[5] Chasis, H. and Smith, H. W : The excretion of urea in normal man and in subjects with glomerulonephritis. J. Clin. Invest , **17**: 347, 1938.

The fact that these simple tests give no indication of the adequacy of tubular function needs no elaboration. While it may seem ill-advised to try to obtain a percentage evaluation of effective renal plasma flow (C_{PAH}) from as uncontrolled a procedure as a PSP test, there does appear to be a very rough correlation as one would expect since both PAH and PSP are eliminated by the same mechanism. However, it is now patently deceptive to try to make an interpretation of the PSP test in terms of per cent of normal function.

As an example of the deception of this test we cite the following case: L. C., an 18 year old white man with progressive glomerulo-tubular nephritis exhibited the laboratory data presented in table 1. In November 1948, he had just recovered from the acute onset of the disease and in July 1949, he had another acute exacerbation with increased loss of function. In October 1949, he appeared to have a remission but his tubular function and glomerular filtration rate were still depressed. On all three occasions the PSP excretion was below normal but was remarkably consistent in the presence of progressive loss of function. The patient died in May 1950.

CONCLUSION

We conclude that neither the urea clearance nor the phenolsulfonphthalein test gives reliable results in terms of per cent of normal glomerular filtration rate, effective renal plasma flow, or excretory tubular function. This study is not intended to shake the faith of those who must continue to rely on these tests as their best measures of glomerular and tubular function, but rather to encourage a more realistic appreciation of just how accurate these studies are. Scrupulous attention to accuracy of timing and urine collection cannot be too strongly emphasized.

SUMMARY

Urea clearance and inulin clearance are compared in 115 tests. The 15 minute excretion of 6 mg. of intravenous PSP is compared to PAH TM in 43 tests and to PAH clearance in 56 patients. The 60 minute excretion of PSP to PAH clearance are compared in 61 patients.

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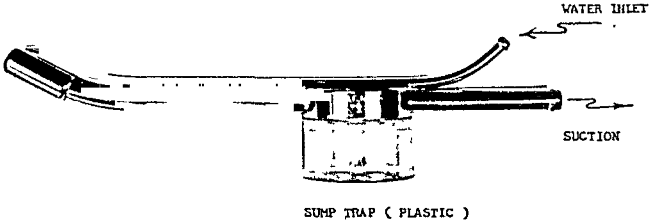
THE HYDRO-VAC

WILFORD A. H. COUNCILL, JR.

From the Department of Urology, University of Virginia Hospital, Charlottesville, Va.

One of the most difficult procedures in renal surgery is the complete removal of fragments of large renal calculi which have been broken off during the manipulative attempt at removal. Calcareous material, too small to be palpated with the gloved finger, must certainly provide a nidus for further precipitation of urinary salts and subsequent reformation of stones.

In an attempt to provide a better instrument for dealing with this situation, a simple and inexpensive device has been designed employing the two principles of suction and lavage functioning concurrently in a single element. The instrument uses the usual operating room suction apparatus and an irrigating flask, both of which are always available. The Hydro-Vac is of stainless steel construction and is approximately eight inches long. It consists of three main parts: a water inlet tube, a suction tube and a sump bowl and trap (fig. 1). The water inlet tube provides a constant medium for agitation and flotation of stone particles. The stream is directed to the most distal point of the instrument and so sets in motion those particles entrapped within the periphery of the suction tip. The suction portion is a tube approximately 0.7 cm. in diameter which is connected to the surgical suction machine. This diameter allows passage of small stones which when aspirated are deflected from the direction of flow into the sump trap.



TECHNIQUE

The Hydro-Vac is inserted into the pyelotomy incision and the tip of the instrument advanced gently toward the infundibulum of the affected calyx and the combined filling and evacuation procedure begun. During the manipulative process the rubber suction tube may be compressed intermittently to allow over filling and increased turbulence of the calcareous material. Release of the suc-

Accepted for publication December 5, 1952.

tion tube with the pelvis filled thereby enhances the possibility of complete stone removal.

SUMMARY

A new instrument has been presented to assist the urologist in his attempt to remove small stones or the products of morcellement incident to pyelolithotomy. The instrument is small enough to be inserted into the pyelotomy and yet large enough to be easily manipulated in the operative site.

The writer wishes to express his thanks to Mr. Frederick J. Wallace of American Cystoscope Makers, Inc. for his kind assistance in the development of the Hydro-Vac.

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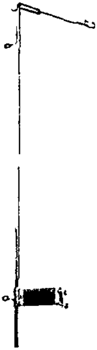
KNEE-ACTION CORD HOLDER

EARL F CUMMINGS

Water, power and light must be readily accessible for surgical procedures when using any type of endoscope, whether in the urinary bladder and prostate or in the vagina or rectum The mechanical equipment pictured (fig 1) and described herewith, has been found practical, simple and convenient during the past 2 years

The spring-arm with loop guides holds the cords firmly in a convenient position for the surgeon, and yet allows a delicate knee action response to any change of position, without tension The spring arm fits into a stationary upright steel tube which is easily adjusted by 2 thumb screws to any desirable height, and will accommodate the operator in either the standing or sitting position



The supporting tube is fixed to the side of the operating table by a small arm held with 2 metal screws Fastening this tube firmly to the table is accomplished by two ¼ inch holes drilled through the table frame This attachment is both simple and small, and readily adaptable to most of the cystoscopic tables in popular use today In order to be out of the way this cord holder should be attached to that side of the table which is opposite to the X ray Bucky mechanism

This instrument is constructed throughout of stainless steel, and is demountable so that the knee action arm may be readily sterilized by autoclaving, boiling or in cold solution

Use of this cord holder eliminates any need for having the cords held by a nurse or attendant, avoids such improvisations as rubber bands or rigid supports, and most important, it keeps the cords from coming in contact with the patient

19 Jefferson Ave , Oshkosh, Wis

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SECTION MEETINGS

Mid-Atlantic Section—Shoreham Hotel, Washington, D. C., April 22-24, 1954
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Southeastern Section—Whitehall Hotel, Palm Beach, Fla., April 12-15, 1954
Western Section—Empress Hotel, Victoria. B. C., Canada, April 19-22, 1954
North Central Section—Detroit, Mich., October 7-9, 1954
South Central Section—Colorado Springs, Colo., October 18-20, 1954

Members of executive committees of Sections, and officers and members of executive committees of Branch Societies are listed on pp. 982-984, December 1953 issue

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INTERRELATIONSHIP OF RENAL CYSTS AND TUMORS
REPORT OF THREE CASES

THOMAS E GIBSON

Probably no organ in the body is more subject to cyst formation than the kidney These cysts assume such startling proportions and infinite variety that they have long been the subject of fascinating speculation as to their etiology and pathogenesis Beneventi in his schematic diagram illustrates twelve different types of renal cysts Even then he does not include echinococcus cysts and the most bizarre manifestation of all, polycystic disease of the kidney Obviously no single theory of origin will suffice to explain the multiplicity of cyst types I do not propose to try to elucidate or even enumerate the many theories of origin, but wish to confine my remarks to one phase of the problem, namely the established clinical relationship of cysts and tumors, and certain deductions from proved experimental facts as they relate to this problem

The following 3 case reports will serve to illustrate this relationship The rarity and unique character of the first case is of especial interest

CASE REPORTS

Case 1. A white woman 53 years of age entered St Josephs Hospital March 23, 1950, with the complaint that 3 days previously while making up her bed she felt something snap in the right sacro iliac region Pain in this region persisted, particularly with movement of the spine and walking There was no radiation, or increased pain on coughing Physical examination revealed a rather obese woman with essentially negative findings except for an incisional hernia which followed appendectomy complicated by peritonitis fifteen years ago Blood pressure was 180 systolic, 94 diastolic Urine analysis was negative. Blood studies were within normal limits and serology negative Sedimentation rate was normal She was discharged following orthopedic consultation

She re entered the hospital on November 1, 1950, approximately eight months later, complaining of a tumor mass in her abdomen which was causing discomfort because of its size She had noticed it for about one month At this time her blood pressure was 160 systolic and 80 diastolic A roentgenogram of the chest was negative Physical examination revealed an enormous smooth abdominal mass, not in the least tender, which suggested a full term pregnancy except that it appeared to arise in the left upper quadrant of the abdomen The mass seemed to increase noticeably in size from day to day A complete urological investigation was done which showed a grotesque distortion of the left kidney in the pyelograms (fig 1) consistent with a tumor so large that it displaced the opposite kidney The indigo carmine concentration in the urine from both kidneys was excellent although there was a slightly delayed appearance time on the left

Left nephrectomy was performed November 5, 1950 On exposing the kidney

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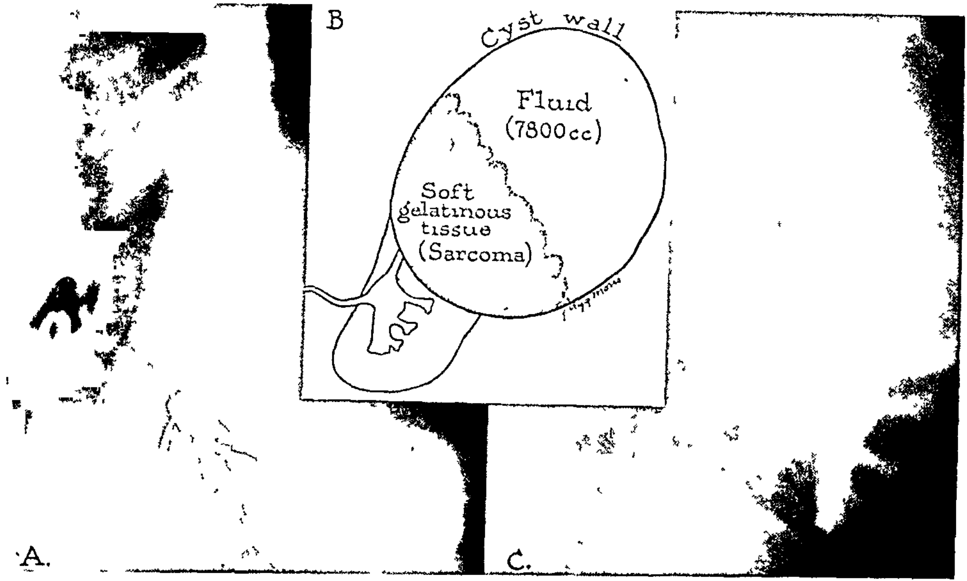

FIG. 1. Case 1. *A*, bilateral pyelograms showing displacement of left kidney and pyelographic defect due to large sarcomatous cyst of left kidney. Right pyelogram shows displacement of right kidney by left renal tumor. *C*, over-injected left pyelogram made in lateral oblique position. *B*, sketch of specimen illustrating giant cyst containing tumor.

through a flank incision the presenting surface of the mass suggested the presence of a gigantic solitary cyst of the kidney. Accordingly, a large trocar was inserted through the cyst wall and a large amount of brownish hemorrhagic fluid was evacuated. The cyst wall was so adherent to the diaphragm and peritoneum that it was separated only with great difficulty, and could not be accomplished without tearing into the cyst cavity. After all the fluid was evacuated the mesial wall of the cyst at its area of attachment to the renal parenchyma was found covered with an extensive growth, resembling a solidified mass of gelatin. A large quantity of this material (which on frozen section proved to be sarcoma) was scooped out of the cyst cavity to reduce its size. The mass including the kidney was then easily removed.

The patient, in spite of the size of the tumor, and difficulty of removal, had a remarkably smooth convalescence and was discharged with her wound healed on the ninth postoperative day.

The specimen was examined by the pathologist, Dr. G. C. Lake, who noted that the sum total of fluid in the cyst was 7800 cc and that the total weight of cyst fluid plus tumor mass was 9640 gm., or a little over twenty one pounds. The mass appeared to arise in the renal parenchyma, the upper pole of the kidney being nearly all destroyed while the lower pole was intact. There was a fairly sharp line of demarcation between the cyst wall and kidney substance, and no connection between the renal pelvic mucosa and the tumor was made out. The report on the histologic features of the tumor was as follows: "Microscopic: Sections from several areas of the solid tumor, from the junction zone of the kidney, and from the cyst wall were examined. The most characteristic feature of all the sections is the presence in some portion of the section of a spindle cell

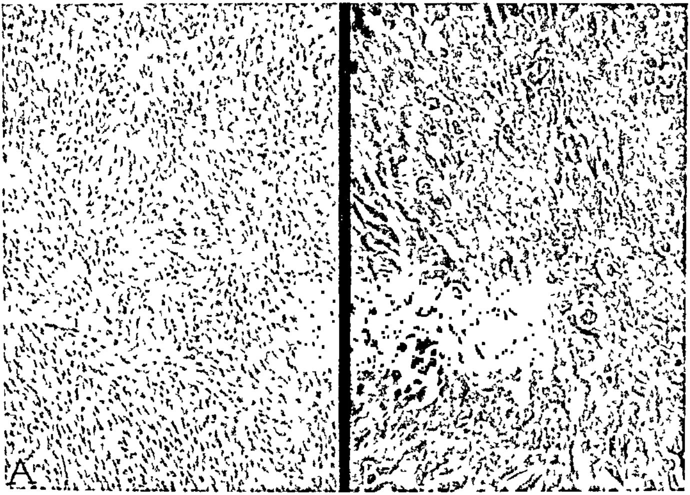

FIG. 2. Case 1. *A*, Low power. *B*, High power microphotographs of tumor from medial wall of cyst showing its sarcomatous character (mesoblastic nephroma)

formation (fig. 2) similar to that seen in the first frozen sections. Invasion of the growth into the kidney tissue is slight and in most areas it is separated by the dense capsule. In the spindle cell growth there are occasional small tubular or cystic structures apparently lined by some type of epithelium; however, there does not seem to be sufficient structural characteristics in the sections to warrant an opinion as to the origin of the tissue. Tentative diagnosis: A cystic tumor of the kidney with marked degenerative changes, possibly a very atypical primary kidney tumor or possibly of some other origin invading the kidney and apparently sarcomatous in character."

The highly malignant character of this cystic tumor is shown by the fact that the patient died approximately one year following operation with roentgenographic evidence of lung metastases, metatasis to the right humerus, and local recurrence in the abdomen. A nodule removed from the anterior end of the incisional scar showed the histologic structure of the primary tumor.

Pathogenesis. About 7 per cent of solitary cysts of the kidney contain neoplastic proliferations. The fluid content is usually clear and serous in type, but may be hemorrhagic as a result of trauma to a pre-existing lesion, proliferative growth of the interior cyst lining, or malignant degeneration (Kutzman and Sauer). In the series of 249 cases collected by Hepler thirty-seven were hemorrhagic, and in the series of Braasch and Hendrick eleven of 163 cases. Lowsley and Curtis state that as high as 25 per cent of hemorrhagic cysts contain malignant elements It is therefore of paramount clinical importance to keep in mind the possibility of malignancy when a hemorrhagic cyst is encountered. The fluid content may be either frankly bloody or chocolate brown as was the case in this patient. Abeshouse states that serous cysts usually increase slowly in size, but cites some notable exceptions in which the cyst assumed tremendous proportions with alarming rapidity. This, I believe, is more apt to happen in the case of hemorrhagic cysts. Obviously, in my case the increase in size had been very rapid and terminally a day to day augmentation was evident. Although my case, because of its rather uniform histologic structure, is called a fibrosarcoma, it has occasional elements suggestive of Wilms's tumor. Culp and Hartman have shown in an excellent clinicopathologic study of Wilms's tumors and related neoplasms that they are all closely related and have a common origin. They recommend that these tumors be called *mesoblastic nephromas,* and the term *Wilms's tumor* abandoned. Their derivation from embryonal mesenchyme whether they are so-called Wilms's tumors or whether they show a more uniform structure, such as the case I am reporting, seems the most logical explanation of their origin. Like testicular tumors, these tumors of the kidney have an inherent potential for mixed histology but occasionally one cell type may predominate. Seminoma of the testis, for example, often seems to be a pure unicellular type of growth, but meticulous search will reveal other diverse elements. Reference above to the pathologist's report indicates the presence of other cellular structures in the tumor which is the subject of this report although on superficial examination it would appear to be a pure spindle cell sarcoma.

*Case 2.** Well developed and nourished white male, age 37 years, entered hospital February 8, 1952 with complaint of sudden severe pain in right costovertebral angle associated with gross total hematuria which began 5 days before entry. On entry the pain had subsided except for moderate tenderness in the costovertebral angle. Urine specimens were grossly blood tinged. Excretory urography revealed a large right renal shadow and total absence of function on the right (fig. 3). A retrograde study showed an abnormal right pyelogram consistent with renal tumor involving the upper pole of the kidney. There were no other abnormal physical or laboratory findings. On February 12, 1952, under pentothal-curare anesthesia, a transperitoneal right nephrectomy was done without appreciable difficulty. The patient was out of bed on the second postoperative day and had an uneventful recovery. The specimen is illustrated in figure 4. The pathologist's report was as follows: "Gross: The specimen consists of a kidney weighing 310 grams and measuring 11 cm. in length by 10 cm. in width across the upper pole, 6 cm. width across the lower pole, 8 cm. in thickness across the upper pole and 5 cm. in thickness across the lower pole. A moderate amount of perirenal fat is [illegible] to the surface and is adherent over the upper pole. When trimmed a[illegible] ous thin walled cysts are seen beneath the capsule the upper pole [illegible] y. The lower half presents a normal external ap- [illegible] ance. The ca[illegible] readily from the lower half of the kidney but is [illegible] nt to the up[illegible] sanc[illegible] a yellowish-orange tumor mass, [illegible] d with red is[illegible] ng the [illegible] yma near the pelvis and base of

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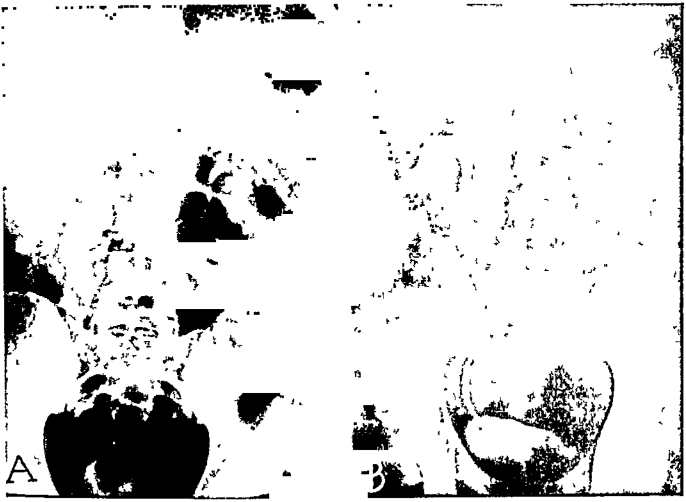


FIG. 3. Case 2. *A*, excretion urogram showing large right renal shadow with total absence of function on the right. *B*, right retrograde pyelogram showing deformity characteristic of renal tumor.

the superior calyx. The superior calyx is markedly distorted and numerous large cysts filled with a clear yellow fluid are seen throughout the upper pole not communicating with the pelvis. The mucosa lining the calyces and pelvis is bluish-grey and shows numerous areas of submucosal hemorrhage. There is no evidence of the tumor arising from or growing through the mucosal lining of the calyces or pelvis. The tumor mass is rather lobular, one portion extending to within less than 2 cm. of the surface and measuring 2 cm. in greatest diameter. Another small lobule extends inward and upward toward the superior calyx and measures approximately 1.5 cm. in diameter. The hemorrhagic discoloration of the pelvic mucosa extends into the upper portion of the ureter for a distance of about 2 cm. The distal 4 cm. of ureter submitted shows no abnormality in the mucosa or in the wall. Dissection of the pelvis reveals no extension of tumor along any of the renal vessels.

"Microscopic: Sections through the tumor show large masses of neoplastic epithelial cells growing for the most part in a papillary pattern but occasionally appearing as gland-like structures. Coarse fibrous trabeculae extend irregularly through the tumor and the tumor cells have a network of rather delicate connective tissue, at times containing large distended blood vessels. Most of the cells are large, pale staining and vacuolated, but in places the cells are smaller, more darkly eosinophilic and granular. The nuclei show moderate variation in size, shape, and chromaticity. Some are small and pyknotic, others large and vesicular. Moderate numbers of mitoses are seen. The expansile growth of the

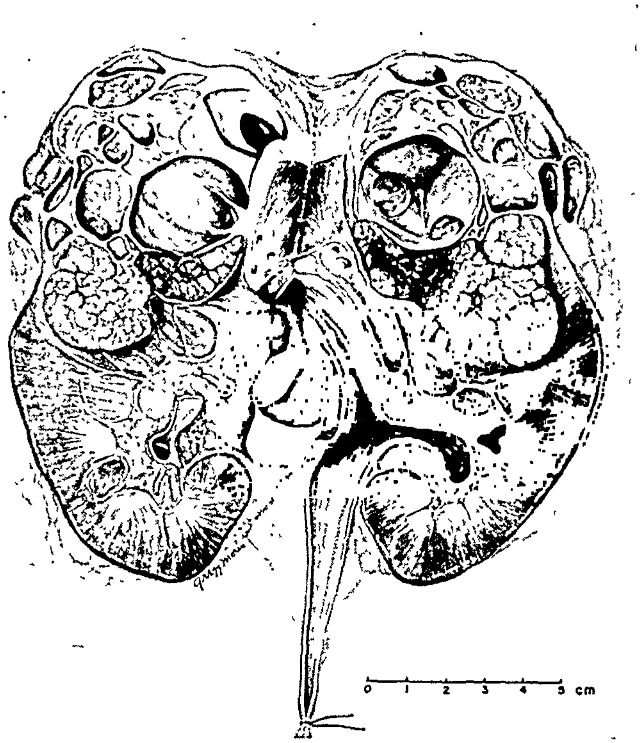


FIG. 4. Case 2. Drawing illustrating clear cell carcinoma of right kidney with multiple cysts distal or peripheral to the tumor.

tumor compresses the adjacent kidney parenchyma in which there is atrophy of the tubules, interstitial fibrosis, round cell infiltration and scattered hyalinized glomeruli. In many places the tumor is necrotic and contains large areas of hemorrhage and cystic degeneration with the cavities sometimes filled with granular eosinophilic material and at other times being empty. The cystic spaces in the upper pole of the kidney appear to have been formed by tumor necrosis. The tumor appears to be well encapsulated but has a lobular outline with trabeculae extending into the tumor tissue from the surrounding fibrous tissue. These trabeculae at times contain atrophic renal tubules and glomeruli. No direct growth of tumor cells into blood vessels is noted in the sections examined. The tumor extends to within less than 2 mm. of the cortex at one point and to within less than 1 mm. of the transitional epithelium lining the calyces. However, the tumor does not extend through the peripelvic fibrous tissue, the epithelial lining or into the peripelvic fat. Diagnosis: Carcinoma, right kidney (clear cell type)."

Case 3. A white man, aged 64 years, complained of "gas pains" for past 15 years. Cholecystectomy was performed in September 1945, but failed to relieve his abdominal distress. At time of operation he was told he had several small cysts in the right kidney which should not give him further trouble. Continued gastro-intestinal symptoms led to a check-up in May 1949 at which time x-ray studies disclosed an ulcer crater in the superior portion of the duodenal cap, also a diverticulum arising from the second portion of the duodenum. A large shadow

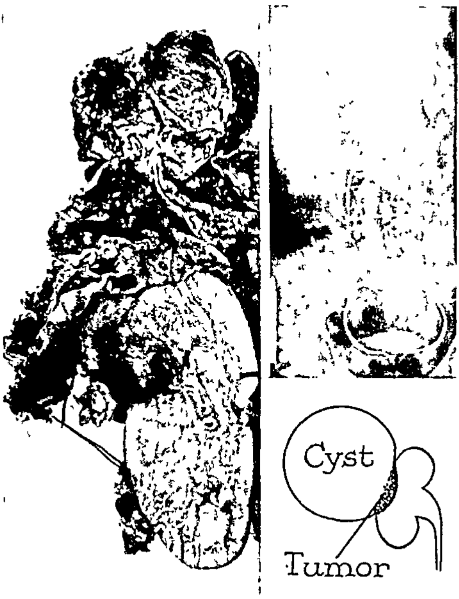


FIG. 5. Case 3. Retrograde pyelograms (upper right) showing large right renal mass with pelvis displ[illegible]ht kidney sectioned showing large collapsed cyst. [illegible] (lower right) shows relation of cyst to kidney with [illegible] its mesial wall.

was noted incidentally in the right upper quadrant which was thought to be an enlarged kidney. Although he had no genito-urinary symptoms a complete urological investigation was done which revealed typical pyelographic changes of renal tumor (fig. 5). An upper right transverse abdominal incision was made, and nephrectomy accomplished transperitoneally. A large cystic mass was encountered protruding from the upper outer border of the kidney. Unfortunately this was accidentally opened liberating some 600 cc of very dark brownish fluid. On examination of the specimen after removal, the base of the cyst at its point of origin in the kidney was seen to have sessile lesions which on microscopic study proved to be granular celled carcinoma of the kidney. The patient made a good recovery and when seen four months later was much improved in health and spirits.

COMMENT

Analysis of the relationships that exist between solitary cysts of the kidney and malignant tumors suggest four possibilities: 1) Unrelated origin of cyst and tumor; 2) origin of a cyst within a tumor; 3) origin of a tumor within a cyst; 4) origin of a cyst distal to a tumor.

A careful study of the pathogenesis of renal cysts leads one to the conclusion that all four of these possibilities exist and can be demonstrated beyond question of reasonable doubt.

1) The finding of a tumor in one pole of a kidney and a cyst in the opposite pole can only be interpreted as a fortuitous coincidence.

2) Cystic degeneration within a tumor is a common and characteristic finding, and is well exemplified in Wilms's tumors of the kidney and malignancies elsewhere such as teratoma testis. Such cysts are entirely different in appearance from the solitary cyst of the kidney containing a tumor apparently arising from the wall of the cyst.

3) A tumor arising directly from the wall of a solitary cyst is a theoretical possibility and probably occurs, but experimental considerations and close scrutiny of clinical material strongly support the conclusion that the great majority of these belong in category 4, because, as will be shown, the tumor arises in the parenchyma causing a cyst to form peripherally which later engulfs the tumor and gives it the deceptive appearance of arising from the cyst wall.

4) Finally, there is the cyst which occurs immediately distal or peripheral to a tumor in the kidney. This is to me the most engrossing and fascinating aspect of cyst formation because the mechanism whereby such cysts are formed can be experimentally reproduced so convincingly in the laboratory.

Some thirty years ago while I was engaged at the University of California in studying the effects of renal tubular obstruction by ligating the papilla of the

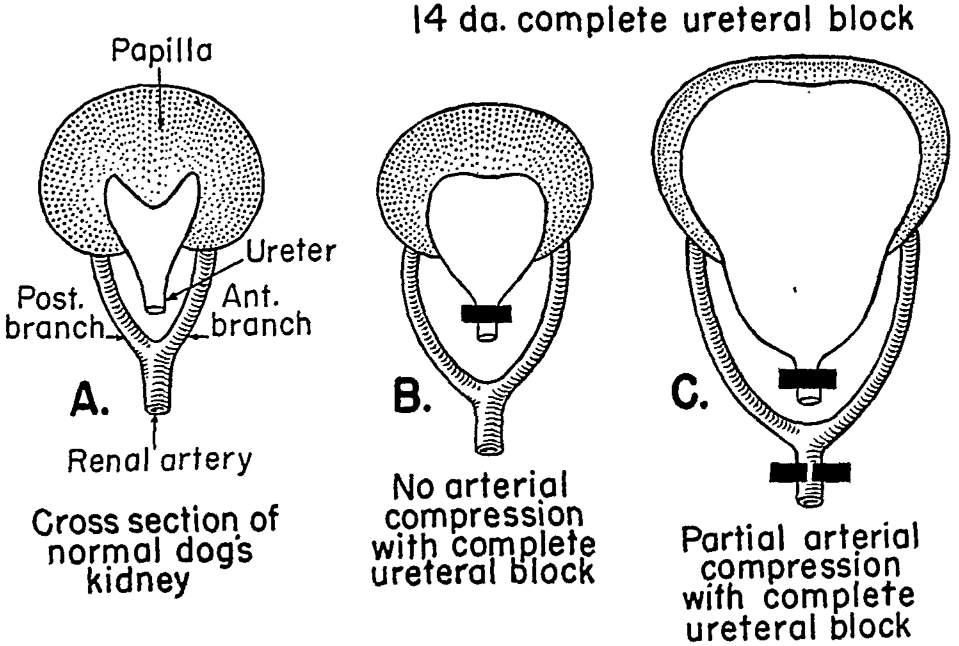
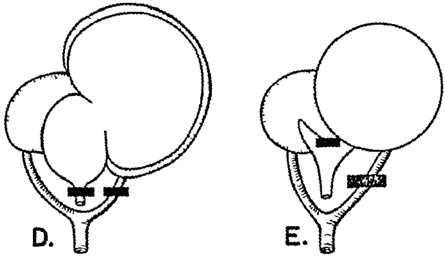

14 da. complete ureteral block
Papilla
Ureter
Post. branch
Ant. branch
A.
Renal artery
Cross section of normal dog's kidney
B.
No arterial compression with complete ureteral block
C.
Partial arterial compression with complete ureteral block

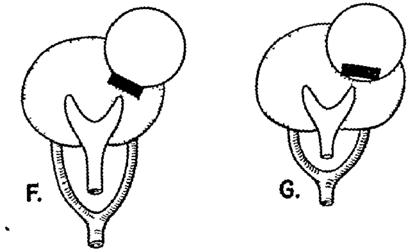
FIG. 6. Experimental hydronephrosis. *A*, cross section of normal dog's kidney, *B*, complete ureteral obstruction of 14 days' duration causing hydronephrosis. *C*, complete ureteral obstruction of 14 days' duration with partial compression of renal artery. Compare *B* and *C* noting marked relative increased dilatation of renal pelvis when complete ureteral block is associated with ischemia caused by compression of renal artery.



D. Complete block of ureter and one branch of renal artery

E. Formation of solitary cyst by tubular block at level of renal papilla and complete block of one branch of renal artery

FIG 7 Experimental hydronephrosis *D*, complete block of ureter and one branch of renal artery causes marked relative disproportion in dilatation of renal pelvis Hydronephrosis is moderate in the renal segment with intact blood supply, but quite marked in the segment where ischemia has been produced by compression of the corresponding branch of renal artery *E*, ligation or fulguration of the renal papilla results only in microscopic dilatation of the renal tubules in the segment where the blood supply is not disturbed but in the opposite segment with arterial block a large solitary cyst forms with great rapidity



Mechanism of cyst formation by tumor, producing combined tubular and arterial block in renal medulla. Tumor may be outside cyst wall or incorporated in cyst wall

FIG 8 Experimental production of solitary cysts offers plausible clinical explanation of interrelationship of solitary cysts associated with renal tumors A tumor arising in the renal parenchyma (*F*) presumably causes combined tubular and vascular block with resultant cyst formation distal to tumor In time original tumor may become involved in compression atrophy and together with the compressed surrounding parenchyma form wall of cyst (*G*) Thus tumor which at operation appears to have arisen from cyst wall actually had its origin in parenchyma mesial to the cyst wall

rabbit's kidney, Hepler working in the same laboratory conceived the ingenious idea of not only producing tubular obstruction by ligation or fulguration of the renal papilla but also of producing ischemia of a corresponding segment of the kidney by partial or total occlusion of a branch of the renal artery Simple tubular

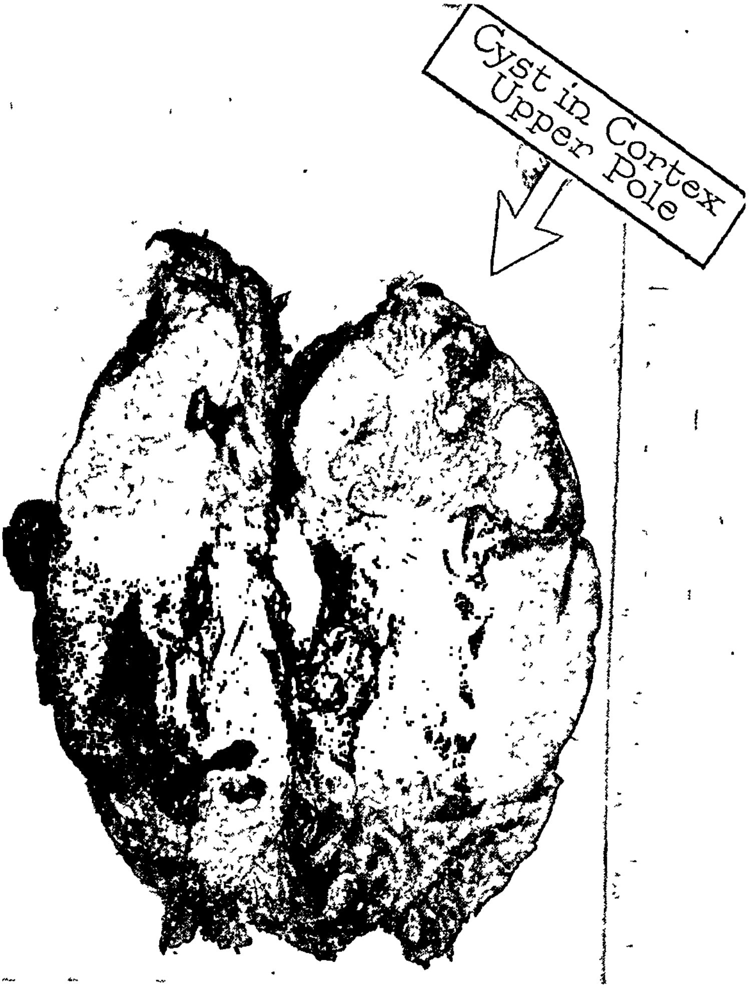


FIG. 9. Tuberculosis of kidney with cyst formation in upper pole. This is not a caseocavernous area but a definite non-tuberculous solitary cyst formed persumably by combined tubular and vascular occlusion as a result of tuberculous lesions medial to cyst wall.

obstruction produced only varying degrees of tubular dilatation but combined tubular and vascular block resulted in the formation of a large solitary cyst with amazing rapidity. Hepler's meticulous work was published in 1930 and since then has been generally accepted as an explanation and elucidation of the mechanism of origin of many renal cysts encountered clinically. The results of combined ureteral or tubular obstruction and vascular occlusion produced experimentally are shown diagramatically in figures 6, 7 and 8. With this experimental background, it is easy to envision the pathogenesis of many renal cysts encountered clinically. Atherosclerotic lesions, tuberculosis (fig. 9), emboli, infarcts, tumors or other pathologic condition so situated in the kidney as to cause group tubular block and vascular occlusion could conceivably result in cyst formation. In the case of a tumor situated in the medulla, combined tubular and vascular block would result in cyst formation distal to the tumor, as in cases 2 and 3 As the cyst enlarges it could conceivably engulf the tumor so that the latter becomes incorporated in the wall of the cyst forming its base This is the probable explanation of the large cyst formation occurring in case 1 Such cysts are usually hemorrhagic because of the tendency for tumors to bleed In many cases the cyst appears to grow at the expense of the tumor since many solitary hemorrhagic cysts are reported in which only small remnants of tumor tissue can be found in the cyst wall A rapidly growing cyst would be more apt to result in compression atrophy of the tumor Hepler cites the case of a cyst the size of a grapefruit which increased to that of a full term pregnancy in two months In case 1 of my report the patient on physical examination had no palpable abdominal tumor 8 months previously and yet at the time of operation it weighed 21 pounds During the last three or four days before operation it appeared to show a daily increase in size Neff collected 5 cases of solitary cyst containing large quantities of fluid (Cassioli) 12 liters, (Lockyer) 25 pints, (Lamson) 11 to 12 quarts, (Krogius) 10 liters and (Archer) 9 quarts He reports a personal case of massive hemorrhagic cyst in a Wilms's tumor of the kidney weighing thirty pounds which was rapidly growing He accepts Hepler's explanation of pathogenesis as the probable one in his case The close similarity between his case and case 1 in my series suggest a similar etiology Gutierrez has reported a similar case in an 18 year old girl, the cyst containing 5 liters of fluid and the remnants of a Wilms's tumor in the wall of the cyst at its base

Walsh who has reviewed over 500 cases of cystic disease of the kidney, found the incidence of malignant tumor to be 7 per cent In hemorrhagic cysts the incidence of associated neoplasm was 30 per cent He concludes that a closer relationship exists between cystic disease of the kidney and tumor than can be explained on the grounds of mere coincidence He favors Hepler's theory, and notes that in cases of associated cyst and neoplasm the neoplasm impinges on the base of the cyst in nearly all of them

In conclusion the lesson to be drawn from this presentation is that solitary cysts of the kidney should never be regarded lightly, but should all be explored with the idea of malignancy in mind, and that they deserve more than cursory examination because of the possibility of small remnants of tumor tissue lurking at the base of the cyst or of actual neoplasm located in the parenchyma medial to the cyst wall

CONCLUSIONS

Three cases of cystic disease of the kidney associated with malignancy are reported

The association of renal cysts and tumors of the kidney is of such frequency as to suggest a causal interrelationship

The experimental production of renal cysts by means of combined renal tubular and vascular block appears to be reproduced clinically by many renal tumors which are found in association with cystic disease

The clinical application of this concept stresses the importance of investi gating every case of cystic disease of the kidney for associated malignancy either within the cyst, where it may exist only as minute remnants at the base of the cyst wall, or as a well defined growth outside and medial to the cyst wall.

450 Sutter St., San Francisco 8, Calif.

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SOLITARY CYSTS OF THE KIDNEY REPORT OF A CASE IN AN INFANT

E H TRAVERS

Recent literature contains few references to solitary cysts of the kidney Moss (1943) classifies cysts of the kidney and accepts Kampmeier's theory of their origin from embryonic provisional nephrons which normally pass through a cystic stage before they finally disappear He states that diagnosis is usually made in middle life and that cysts are very infrequent in infants He quotes a series of 32 cases in which the youngest patient was 19 years of age

Loeb (1943) refers to Kampmeier's theory and to Hepler's experimental production of cysts by a combination of tubular obstruction and local ischemia He suggests that both congenital and acquired factors may play a part He describes three cases, all with complications

Fister (1943) states that the solitary cyst may be congenital or acquired but that the mechanism of production is the same and consists of a tubular defect or damage associated with a local vascular disturbance In a series of 5 cases the youngest patient was 6 years old

Chalkley and Sutton (1943) state that solitary cysts are rare in children They refer to 10 collected cases and add one of their own Of these eleven, one cyst followed an injury, another was probably a hydronephrotic sac and a third was associated with hydronephrosis and a tuberculous cavity in the kidney Two patients in the series were aged 1 year, one, 13 months, one, 2 years, one, 3 years, and the others 4½ (hydronephrosis), 6 (accident), 8, 10, 11, 13 and 13 (hydronephrosis and tuberculosis) years respectively

Abbey Smith (1948) refers to over 300 cases and states that 75 per cent were diagnosed in the fifth decade He describes 1 case in a man of eighteen Herbst and Polkey (1937) describe 4 cases, all in adults

Aird (1949) states that nearly all cases of this condition have been adult and that the chief difficulty in diagnosis is from retroperitoneal sarcoma Morson (1948) states that the evidence is in favor of an acquired as opposed to a congenital etiology and classifies the condition accordingly He adds that these cysts are invariably found in those of advanced years and that they are rare

The following case of a solitary cyst in an infant, who was operated upon at the age of 4 weeks, appears worth placing on record as no reference has been found to a patient's suffering from this condition at such an early age The case would, perhaps, tend to support the view that the condition is of developmental origin

CASE REPORT

Susan H , aged 4 weeks, was admitted to the hospital on November 28, 1950 under the care of Dr J J Tillie who asked me to see her the following day The baby was born in a nursing home on October 28 at full term Delivery was

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normal and the birth weight 8 pounds, 9 ounces. She was being breast fed 5 times daily. She slept well and the bladder and bowels were acting normally. There had been no vomiting. At birth it was noted that the baby had an unusually large abdomen and she is said to have become cyanosed occasionally during the early days of life. Both parents were healthy as was a sister aged 9 years.

The baby weighed 9 pounds, 13 ounces and appeared healthy apart from the presence of a very large, smooth and rounded tumor filling the right side of the abdomen and expanding the lower chest wall. The tumor was clinically of retroperitoneal origin. A tentative diagnosis of retroperitoneal neuroblastoma or sarcoma was made and exploration advised with, if possible, removal of the tumor. A specimen of urine revealed no abnormality on chemical, microscopic or bacteriological examination. X-ray of the abdomen and chest on December 1 showed an opacity filling the right side and left upper quadrant of the abdomen and a normal chest apart from displacement of the diaphragm.

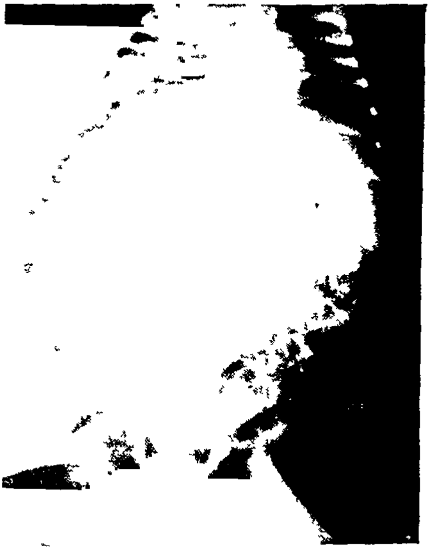

Figure 1

Operation (December 1, 1950): Under open ether anesthesia the abdomen was opened by a long right paramedian incision. A cystic retroperitoneal tumor was identified as representing the right kidney. The left kidney was apparently normal and the opacity noted on x-ray in the left upper quadrant of the abdomen was due to displacement and rotation of the liver. The right ureter was defined stretched over the medial aspect of the tumor and was normal in size. The right suprarenal gland was closely applied to the superior aspect of the tumor. The ureter was ligated and divided. The suprarenal gland was dissected free and returned to the abdomen; it consisted of a thin flat sheet of tissue with a pedicle sufficiently long to allow it to be drawn completely outside the abdomen. At this stage, in order to facilitate further mobilization, the content of the cyst was evacuated. It was then seen that there was rather more substance to the wall of the cyst medially, at which point the renal pedicle was identified, ligated and divided allowing the tumor to be removed The abdomen was closed in layers Approximately 20 ounces of clear colorless fluid had been evacuated from the cyst

The postoperative period was uneventful except for pyrexia on the second day which rapidly subsided with the oral administration of penicillin On December 4 the baby weighed 8 pounds, 8 ounces with the dressing in place She was discharged on December 13 with the wound healed, weighing 9 pounds, 3 ounces and taking her feeds well

Figure 1 shows the x-ray appearance before operation The lining of the cyst was of delicate fibrous tissue devoid of epithelium The renal tissue was compressed with glomeruli in the parts adjacent to the cyst

The patient was examined at the age of 8 months by Dr Tillie and myself and was found to be in excellent health

I wish to thank Dr Tillie, in whose wards this child was treated, for his help and co operation, Dr J E Howell, my anesthetist, Dr David Glass, for the x rays, and Drs Stanley Wray and A N Blades, for the histological examination of the cyst

186, Bishopton Road, Stockton on-Tees, England

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Paroxysmal cold hemoglobinuria occurs in luetics, principally of the congenital type. In 5 per cent of cases there is no evidence of lues. Exposure to cold precipitates a bout of hemoglobinuria associated with aching pains in the back and legs and abdominal cramps. The Donath-Landsteiner test establishes the presence of autohemolysin. In the foregoing four conditions described, the presence of hemosiderin deposits in the renal tubules is extensive. When the tubular cells become so saturated with hemosiderin a reabsorption of hemoglobin is impaired and hemoglobinuria occurs at a relatively low plasma level.

Hemoglobinuria in our case was unilateral, which ruled out the systemic and prerenal causes. The condition was not paroxysmal and was found associated with and complicated by the presence of a renal neoplasm. In that the neoplasm was of both tubular and connective tissue origin, one can readily see the relationship of the alteration of the glomerular circulation as well as that of the tubular epithelium and the possibility of a direct modification of the glomerular capillary cells as a result of the neoplastic change.

RENAL NEOPLASM

Unusual renal tumors have been discussed at great length over the period of years, each with its own case report and separate pathologic classification and with little uniformity. As each mixed tumor of a carcinosarcoma type appeared, the lesion was frequently identified by a descriptive term of its cellular components, making for a large series of tumor types limited only by the combination of tissue elements and cell types found. Culp in 1948 reviewed the literature of mesoblastic tumors and found 53 different diagnoses. After a study of the tumors and their embryological origin he suggested a common relationship and appropriate terminology. The term *Wilms tumor* in the adult has been used and has been associated with the description of the cellular components in the classification. T. D. Moore in 1951 has evaluated this problem and points out the value of classification as described by Culp. It is felt the mesoblastic mixed cell nephroma in the adult is a more accurate classification of this type of tumor. One should be able to demonstrate carcinoma-like cells in tubular, cylindrical, papillary or solid arrangement. Sarcomatous elements must also be demonstrated which would include the oval or round spindle cell.

In that these tumors are closely related and vary in cellular structure or architectural pattern, a minute morphologic classification becomes unwieldy. Culp points out that of renal neoplasms the major groups are the tumors of the cortex, pelvis and capsule. Malignant tumors arising in the cortex can be grouped as carcinoma arising from mature renal tubules and embryonal tumors from the renal blastema. Pelvic tumors include tumors of the renal pelvis, ureter and the calyceal system and collecting tubules which arise from the mesonephric or wolffian duct. Thus we see, of the embryonal nephroma, two major groups; namely, mesoblastic nephroma, which is of cortical origin, and the mesonephric nephroma, which is related to the collecting system. The mesoblastic nephroma can show a predominant carcinoma or sarcoma type cell, or may be of a mixed cell type, depending on the histologic picture in that the renal blastema is part of the nephrogenic line and contains most primitive mesoderm as well as certain elements of all three basic layers T D Moore in 1951 presented the sixty first case of a mesoblastic mixed cell nephroma It is felt from the histologic picture that this case is one of a mesoblastic nephroma, as described by Culp and by Moore It has been shown that a patient with this type of tumor has a very poor prognosis The one year survival rate has been shown to be the average

CASE REPORT

A 52 year old white woman was admitted to St Francis Hospital, Evanston Illinois, register No 31727, complaining of gross total hematuria of 1 month's duration and associated intermittent lumbosacral pain also for 1 month, most marked on the left side The patient had occasional bouts of frequency and burning on urination for three to four months prior to admission She was otherwise symptom-free until 1 month prior to admission when the back pain and hematuria were noted The childhood history was negative and the family history was not contributory The patient had undergone appendectomy in 1918 No other major surgery was performed She had passed the period of menopause 5 years prior to admission

Physical examination revealed a well developed, well nourished white woman who was not in pain Her ears, nose and throat were essentially normal Pupils were equal and reacted to light and accommodation Her chest was symmetrical and the lungs clear and resonant Her heart borders were within normal limits, rate 80 per minute, rhythm regular, no murmurs Blood pressure was 135/85 Her abdomen was soft, nontender, no masses palpable The kidneys, liver and spleen were not enlarged Vaginal examination was essentially normal Extremities were normal Neurological examination was negative Her work up included a complete blood count which was within normal limits The blood urea nitrogen was 14, creatinine 1 Urine was clear, red, with pH of 5 5, specific gravity 1 015, 5–6 white blood cells, 4–5 red blood cells, 3 plus test for hemoglobin Subsequent specimens continued to reveal clear red urine which was found to be red when obtained Prophinuria and alkaptonuria were ruled out Urine cultures revealed Aerobacter aerogenes Cystoscopy revealed a complete lack of filling of the superior calyx of the left kidney and was thought to be compatible with renal neoplasm (fig 1) Urine specimens from the left kidney revealed 3 plus hemoglobin with only an occasional red blood cell Clear red urine was seen coming from the left ureteral orifice A left nephrectomy was performed, using the classical left flank approach The kidney was identified in the wound and the renal pedicle was isolated before the kidney was manipulated, inspected and found to be free of a tumor mass This was then doubly clamped and the kidney removed without difficulty The ureter was transected 5 cm from the ureteropelvic junction The wound was closed in layers and good healing resulted

Postoperative chemistry and blood counts remained within normal limits Examination of the tissue removed was described grossly as a left kidney measuring 11 by 4 5 by 3 5 cm The capsule stripped with ease The kidney was sectioned and the cortex was found to be well differentiated and measuring 1 5

FIG. 1. Retrograde pyelogram. Filling defect upper pole of left kidney compatible with parenchymal neoplasm.

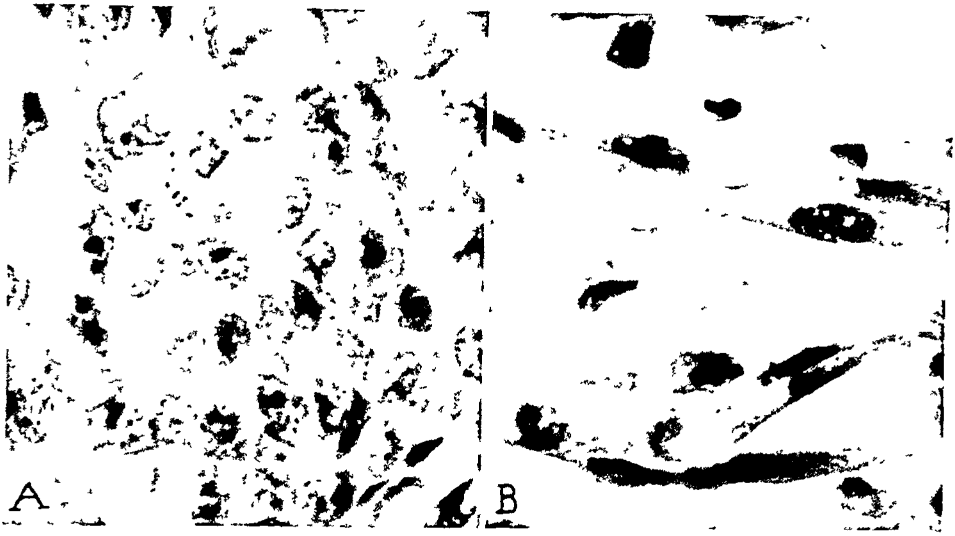

FIG. 2. *A*, Photomicrograph, × 300, of tumor section. Adenocarcinoma. Note hyperchromatic nuclei and abundant mitotic figures. Cells are arranged in sheets with occasional attempts at glandular formation. *B*, photomicrograph, × 300, of tumor tissue, this area showing connective tissue elements with long spindle cells and mitotic figures.

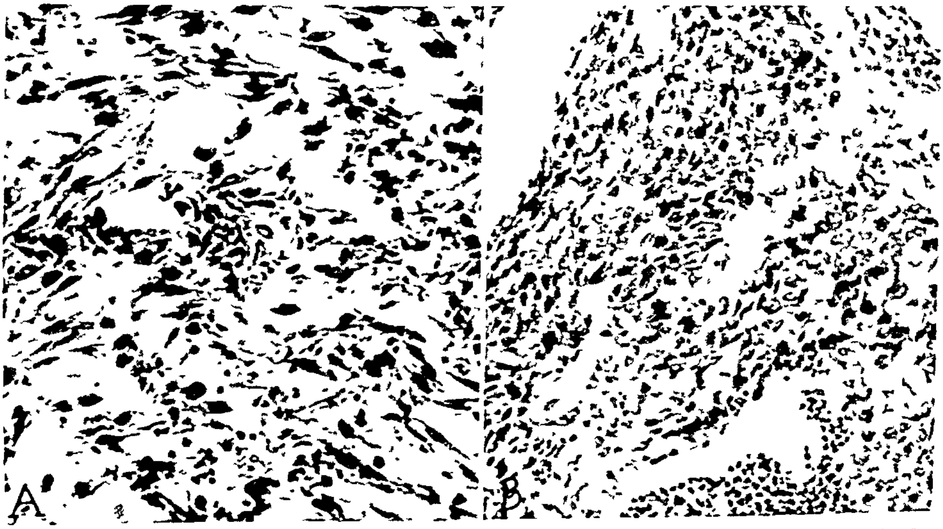

FIG. 3. *A*, photomicrograph, × 150, of tumor section showing areas of combined adenocarcinoma and sarcomatous elements. *B*, photomicrograph, × 150, showing invasion of tumor into renal pyramid with intact transitional cell covering. Note round cells in surrounding tissues.

cm in average width The medullary portion of the middle upper pole contained a tumor mass measuring 2 cm in its greatest diameter which appeared grossly to be a pale transluscent mucoid type tissue The tumor was seen to occlude the infundibulum to the upper calyx The lesion was situated in the parenchyma and caused extrinsic pressure on the draining system Microscopic examination of the sections revealed round or oval spindle shaped cells which were hyperchromatic and found in a diffuse mucoid stroma (fig 2) Frequent mitotic figures were noted within the nuclei Also noted were glandular elements consisting of cells with small granular nuclei demonstrating frequent mitotic figures The arrangement of these cells was primarily in sheets with some attempt at acinar formation (fig 3, *A*) Round cell infiltration was also noted In one area neoplastic invasion of the renal pyramid was noted without disruption of the epithelial covering (fig 3, *B*) The diagnosis was that of a renal neoplasm of the mixed cell type demonstrating carcinosarcoma elements

The postoperative course was uneventful and the patient returned home on the fourteenth postoperative day Approximately 1 month following surgery a sinus tract developed at the operative site with extensive granulation tissue and development of local as well as distant metastatic spread of the neoplasm The patient expired at home approximately six months after the diagnosis had been made

SUMMARY

A case of a mesoblastic nephroma of the mixed cell type in the adult is presented, being complicated by unilateral hemoglobinuria Hemoglobinuria has been reviewed as a clinical entity and the mechanisms predisposing to its production discussed The mechanism responsible for the hemoglobinuria in this case, it is felt, was the tubular and glomerular alterations by the invading neoplasm A discussion and review of the classification of renal neoplasms of the mixed type have been presented and a case of a mesoblastic nephroma added to the literature

University Bldg , Evanston, Ill

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PREGNANCY FOLLOWING TREATED EMBRYONAL TUMOR

H. IVAN BROWN AND PRESTON H. PETERSON
From the Ravenswood Hospital, Chicago, Ill.

This report cites a case of interest to the obstetrician as well as to the urologist. Wilms's tumors are rare in adults, and pregnancy following treatment in an adult case is not found in the literature by the authors. An attempt will be made to summarize in part some of the recent views in relation to Wilms's tumor.

HISTORY

The earliest writings referring to Wilms's tumor were probably by Gairduer in 1828 when he described "fungus hematodes" of the kidney in a child. Priestley suggests this was the earliest writing. In 1872 Eberth described a mixed tissue renal tumor; Kocher and Langhans reported one of them and they were probably the first to be complete in their description. Others up to the present time have been describing adenosarcoma, embryonic carcinoma, mesoblastic adenosarcoma and as many as 50 other terms have been given to Wilms's tumor, according to Culp and Hartman. In 1897, Walker summarized reports of some 142 cases of renal tumors which could have been Wilms's tumors; however, it is probable that many of these were hypernephromas.

Wilms's lengthy article in 1899 stimulated growing interest in this neoplasm. Huber opened the door to treatment by doing the first nephrectomy for embryoma of Wilms.

INCIDENCE

According to textbooks on pathology, embryomas occur chiefly in children before the age of five. Others state it is most frequently seen in the first decade of life. Statistics from the reports available show there is no predilection for sex or side for lesions to occur. Priestley et al. reported that at the Mayo Clinic the incidence was one case in 25,000 admissions. From other centers reports vary widely; however, it is generally accepted that 25 per cent of malignant neoplasms in children are of this type.

Wilms's embryonal tumor is much more rare in adult life. Esersky et al. in 1947 reported 56 cases in the literature and added three of their own. In 1948 Culp and Hartman collected 97 cases of adults that had been reported in the literature.

HISTOGENESIS

Most authors incline toward the theory of Wilms's regarding origin of embryomas. He theorized that implants from a myotome became incorporated in the metanephrogenic ridge and that this implant ceased to grow till a later date. Some became rapid growing, others were slower. Another theory is that there is a disproportionate growth in different elements of the myotome. The most important argument against the myotome theory is the absence of striated muscle in some tissue, Esersky et al. cites this. Cohnheim late in the nineteenth

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century purported a cell rest theory which originated from mesonephric tissue

In studying the many theories one might summarize by saying it may be considered that embryonal renal tumors arise through 1) one or more germ layers, 2) metaplasia and growth of cell rests in embryonal kidney, 3) not uniformly differentiated and with different degrees of sensitivity to radiation

PATHOLOGY

Characteristically embryoma of the kidney reaches a rather large size before metastases occur Then frequently the growth becomes rapid and fatal The tumor is usually encapsulated Glandular tissue, connective tissue, muscle, bone and cartilage are typical A glandular or carcinomatous tumor mixed with a cellular sarcomatous structure is often found Within this may be found remnants of kidney tissue such as a glomerulus or tubule devoid of its supporting structures Thence comes the frequently used term adenosarcoma The capsule previously mentioned is by some considered false as the same tumor structures may develop within it and further metastases take place

Cysts and cystic areas within the tumor are present in many cases In both solid and cystic areas, there is frequently found fatty degeneration and grayish patches of necrosis The diagnosis of Wilms's embryoma is not difficult to make microscopically

Twinem states that in order to diagnose Wilms's tumor histologically carcinoma appearing cells in acinar, tubular or groups with sarcomatous like spindle cells should be found Priestley also believes that this picture is an essential denominator of the tumor

Metastases usually occur to the local lymphatics and extend to the lymphatic glands adjacent to the great vessels Involvement of liver and lungs may be present Metastasis to bone is rare In a series of cases reported by Priestley, twelve out of 44 cases had local recurrence of the tumor after excision of kidney

CLINICAL MANIFESTATIONS

In many cases the first and sometimes only complaint is a mass in the abdomen This is particularly true in children Higgins and Shively report twenty-five of 26 children presented such a history Pain and hematuria are two other important suggestive symptoms in the order of frequency Pain is dull and colicky and varies in different people Temperature elevation was noted in 42 per cent of Higgins' series of children at first examination Other symptoms are sometimes found such as nausea, vomiting, anemia and lassitude Others report significant symptoms as being weight loss, cachexia and anorexia

Laboratory findings may be rather meager, but in a significant number of cases, anemia with hemoglobin as low as 8 gm per cent, mild leukocytosis and mild albuminuria and/or hematuria were found

In adults the signs and symptoms may be somewhat confusing, however, Sparks cites three symptoms that should alert one to investigating the possibility of a renal neoplasm 1) Presence of a large mass, 2) toxemia with elevation of temperature even in the face of no urinary signs, 3) malaise

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tumor in one individual may have a better prognosis than in another The condition is too rare for any group of writers to accumulate enough cases to make significant statistics, but in general the tumor is considered highly malignant both in children and adults

From 1914 to 1923 statistics showed 98 per cent mortality Ladd and co workers from 1932 to 1941 had a mortality of 40 per cent which far surpasses any other reports It is true that most cases show definite metastases by the fifth month Some authors state that if the lesion has not recurred by one year, one might be optimistic about a permanent cure Most writers, however, adhere to the 5 year survival

Through various plans of treatment Gahagen et al cite 35 cases and the report from Lippert totals 36 cases with 5 year cure Culp and Hartman in their article on mesoblastic nephroma in adults report 5 adults in the literature who have a 5-year cure from this type of tumor

CASE REPORT

A 27 year old white woman was admitted to the Ravenswood Hospital with a complaint of severe nausea and vomiting for 3 days Clinical history disclosed diarrhea for one day, pain in back and abdomen, and progressive abdominal distention over a period of 2 years She had no subjective signs referable to the urinary tract In the past there was nothing unusual She had been married 2 years and had never been pregnant The family history was entirely noncontributory

On physical examinations the pulse was 120 per minute The abdomen was distended and flat to percussion everywhere except in the lower abdomen, and no tenderness was noted

The laboratory studies Urinalysis 1 plus albumin, numerous epithelial cells, and few pus cells Complete blood count 9 5 gm hemoglobin, 3,280,000 red cells, 15,050 white cells with 89 per cent polynuclears A plain x ray showed that the upper abdomen was obliterated by a shadow having the density of fluid The hepatic flexure and transverse colon were displaced downward A laparotomy was done on the first hospital day with a reserved preoperative diagnosis A large amount of serosanguinous fluid was removed from what was thought to be a perinephric cyst at the time A diagnosis of an embryonal tumor of Wilms's type was made on biopsy

By means of a transperitoneal route an enlarged kidney was removed

Pathological report "Kidney and attached mass measures 26 by 18 by 8 5 cm The kidney itself measures 13 2 by 7 8 by 7 cm In the upper pole of the kidney there is a firmly attached tissue mass blended in with the kidney substance The mass has a firm fibrous wall about 5 mm in thickness It has a soft necrotic yellow and red content with a fleshy tissue of varying degrees of thickness from 5–20 mm inside the fibrous covering In the wider areas of the wall, small cysts 1–5 cm with gelatinous content are present The outer surface is rough and has many fibrous tags and numerous hemorrhagic areas "

Microscopic examinations ' The wall of the cyst has an inner lining of nu-

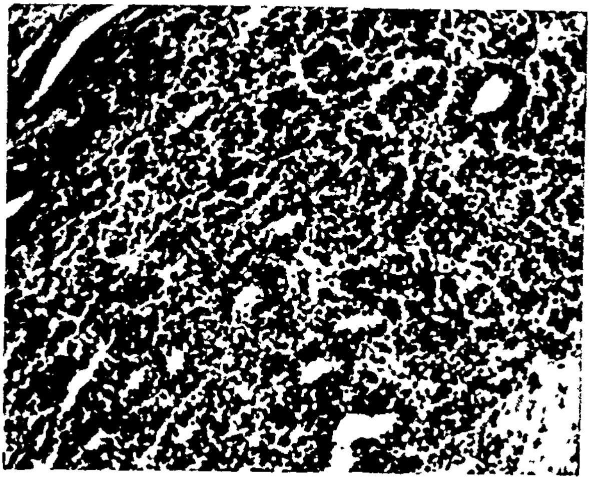

FIG 1

merous small alveoli with an occasional large open space lined by cuboidal cells. Outside of this the wall is dense fibrous tissue with areas of round cell infiltration; irregular portions of kidney tissue are found, some single glomeruli and an occasional tubule. Additional sections from other portions of the soft tissue show acinar and tubular formation of epithelial-like cells surrounded by dense stroma of spindle cells having various sized nuclei. Some portions appear to have relatively normal appearing fibrous tissue while adjacent to this is located more epithelial-like cells and remnants of a glomerulus may be found. The solid alveoli are composed of small, deeply staining cells; as the inner portion is approached, tissue becomes necrotic. In the kidney tissue proper there are numerous deposits of round cells around the glomeruli and between the tubules. Diagnosis: Wilms's tumor that shows inflammatory changes due to long continued drainage."

Radiation was not included in the treatment at any time; and 2½ years later, apparently free of recurrence, the patient had a spontaneous abortion followed by uterine curettage. Pregnancy had progressed 12 weeks. Again, 6 years following the removal of her kidney, she had another spontaneous abortion; gestation was 9 weeks.

After 8 years following the removal of the Wilms's tumor, she was again admitted to the hospital threatening to abort a 12 week fetus. With bedrest and conservative treatment the bleeding subsided. No complicating signs were noted until term when her urine showed a trace of albumin and the blood pressure rose to 142/90. She was admitted to the hospital and in view of the past history, labor was induced. She delivered a full term living infant. Postpartum course was uneventful.

SUMMARY

A case of Wilms's embryoma of kidney in an adult is reported.

A 5-year cure from Wilms's tumor in an adult is reported where 9 years following, the patient delivered a full term normal infant.

Some recent concepts of Wilms's tumors are reviewed.

1045 N. California Stockton, Calif. (P. H.P .)

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BILATERAL RENAL AGENESIS

JACOB FRUMKIN AND RUTH MARZ

From the Department of Pathology, Ellis Hospital, Schenectady, N. Y.

Congenital anomalies of the urinary tract occur very frequently but the absence of both kidneys is a rare abnormality that stimulates interest and curiosity. The discovery of four cases in 230 fetal and neonatal (1–10 days) autopsies for a five year period warranted the report.

Since Coen,[1] in 1883, assembled 32 cases, the total of 166 instances have appeared in the literature: Rosenbaum,[2] Madisson,[3] Amolsch,[4] Hinman,[5] Levin,[6] Guenwardene,[7] Przeworski,[8] Seidel,[9] Grimm,[10] Nation,[11] Stokes,[12] and Potter.[13] Four new cases are added by the authors, which increase the total to 170 cases. This group is further increased by two if we accept Gruenwald's[14] report and Auer's[15] findings of bilateral renal agenesis in the human embryo.

Renal agenesis usually is associated with other organ abnormalities but can occur independently. The early authors ascribe pressure upon the developing embryo, amniotic adhesions, inflammation, hydramnios or oligohydramnios. Although these factors explain the etiology in some cases, the absence of kidneys has occurred without abnormalities in the amniotic fluid. Furthermore, the pressure theory does not account for the normalcy of neighboring organs as the adrenal glands and the dysplasia of the distant tissues as the lower extremities.

Ranier[16] introduced the factor of synergetic influence of the ureteral bud epithelium upon metanephrogenic development. Support for this view is based upon the fact that completely formed kidneys are not recorded in the absence of the ureteral buds. Contrarily, cases have been reported in which the kidneys were absent but the ureters were present in some state of development.

Brown[17] and Boyden[18] have demonstrated that the renal anlage can form an embryonic kidney without development of the ureter by experimental arrest of the wolffian duct. Nation[11] substantiates the observations by stating that resorption of the renal anlage always follows the failure of the ureter to come in contact with the nephrogenic cap. If contact does occur but fusion is improper,

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aplasia usually results In addition, abnormalities of blood vessels might impede the growth of the renal mass or wolffian duct

Madisson[3] attributes anephrogenesis to defective germ plasm on a mutation basis and cites two cases of bilateral renal agenesis occurring in separate pregnancies of the same mother

Arey[19] explained the cause of all kinds of anomalies by a single factor, developmental arrest or inhibition, with the exception of those admittedly hereditary and transmitted through the germ plasm in accordance with laws of genetics Experimentally, Stockard[20] demonstrated that he could produce any anomaly by lowering the temperature or reducing the oxygen supply (lowering oxidation of development) The whole embryo and its component parts do not develop at the same rate There are periods of active growth followed by intervals of slow growth and relative nondifferentiation If arrest occurs during active growth or differentiation of an organ, it would consequently be suppressed and fail to develop Arrest during natural retardation periods results in little or no damage to the organ Riddle[21] agreed with Stockard's conclusion and added that accelerations of metabolism, if occurring at critical stages, are as effective as arrests in causing malformations

Renal agenesis has a definite sex directed tendency The ratio of males to females is 3 07 1 (95 males, 31 females and 42 unclassified) Contrarily Nation[11] states the ratio of ureteral anomalies as 1 male to 4 females

According to Potter[22] bilateral renal agenesis can be diagnosed by typical facial characteristics consisting of increased space between the eyes and the presence of an unusually prominent fold arising at the inner canthus of each eye The facies resemble extreme premature senility with flattening and broadening of the nose, receding chin and large low set ears containing very little cartilage Three of the four cases reported by the authors, as well as Levin's case, did not confirm the typical facial findings In the 20 instances reported by Potter[22] there was no causative relationship of method of delivery, parity, maternal age or complications of pregnancy

Associated malformations of other organs and systems were multiple and variable Dysplasias of the lower extremities were prominent as sirenomelus, apus, monopus and other lesser deformities The terminal large bowel was usually undeveloped and the anus was ordinarily not patent Cases of absence of the upper abdominal viscera, such as the liver, spleen, stomach, and pancreas, were often associated with acrania and abrachia In most instances the adrenal glands were present in the usual site and normal except for alteration of form due to renal absence Occasionally the adrenal glands were reported as hypertrophied

The dysplasias of the genito urinary systems were the predominant features In the male the wolffian duct system was most often affected, whereas in the female the mullerian duct system was influenced. The gonads were commonly present, abnormally formed and often undescended. The prostate and seminal vesicles were reported in some cases, and undeveloped or absent in others. The ureters were usually absent but in a very few cases rudimentary ureters were found as well as microscopic evidence of renal elements. The bladder was present in half of the cases.

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With exception of two instances all cases of bilateral renal agenesis died within hours of birth or were stillborn. The exceptions included one patient who lived 11 days and the other 21 days. Cause of death in practically all was extrarenal. Since an anephric fetus can come to term, kidney function is not necessary for development and growth in utero.

CASE REPORTS

Case 1. (N-49-167) a malformed fetus (Monopus) was delivered stillborn September 8, 1949 about 8 weeks prior to the calculated term. The mother, 23 year old para 1, had epileptiform seizures during the course of the pregnancy. Fetal heart sounds ceased during the second state of labor. All the placental vessels showed extreme congestion on gross and microscopic examination.

The infant displayed a well-formed head, neck, upper torso and upper extremities (fig. 1). It measured 31.5 cm. total length and weighed 1040 gm. The abdomen was elongated, flattened and tapered to a single lower extremity, 17 cm. long. A single pelvic bone projected under the intact skin. The sacrum and coccyx were absent but a dimpling of the skin occupied the pudendal region. There was no evidence of a urethral meatus, scrotal tissue or pudendal folds.

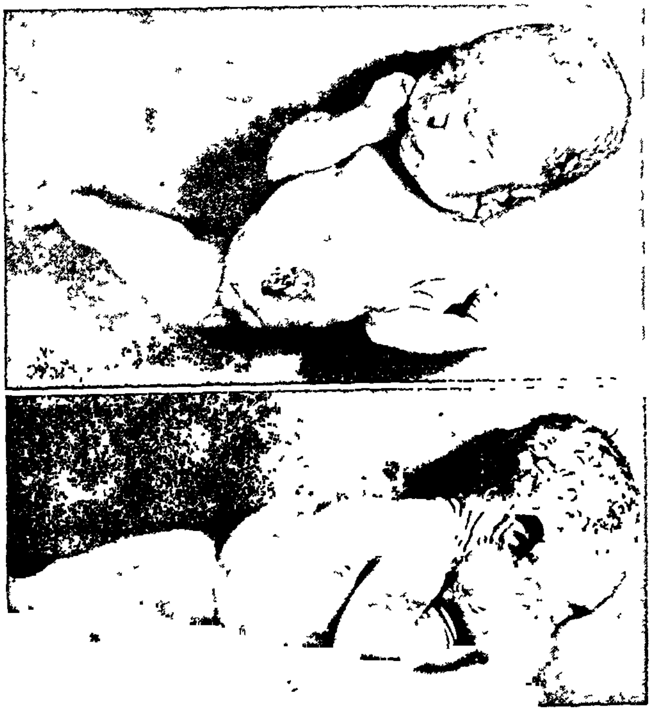

FIG 1 Case 1. Premature monopus with bilateral renal agenesis

X-ray studies demonstrated normal skeletal development of the skull, cervical dorsolumbar spine, thorax and upper extremities The sacrum, coccyx, right ilium and right leg were absent The single femur on the left side was unusually broad in the distal half Two similar bones in the leg resembled tibiae

Dissection disclosed normal head, scalp and skull Meningeal and cerebral vessels were congested but the brain was well developed for the size of the fetus The thoracic cavity and contents were normal except for the small thymus, which weighed one gram The upper abdominal organs including the liver, spleen, stomach and small intestines were not remarkable At the umbilical level the descending colon was constricted and became continuous with the tissue of the urachus, although there was no distinct lumen between the two structures

The ovoid adrenals (4 gm combined weight) were histologically normal Those organs, not identified, were sigmoid, colon, rectum, anus, kidneys, ureters, urinary bladder, uterus, internal genitalia and gonads Distinct tissues pertaining to the urogenital tract were not observed in the prepudendal tissue mass Microscopic studies of the normally developed organs failed to disclose any significant changes Pituitary gland was not available

Case 2 (N-51-165) a 23 year old, Rh positive, gravida 3 had vaginal bleeding at 31 weeks' gestation Spontaneous onset of labor developed 1 week later and she delivered a living, male infant by breech presentation The infant was cyanotic and had repeated episodes of apnea followed by irregular cardiac rhythm The heart ceased 1 hour following delivery Obstetrical history revealed one living child born in 1949 and one late abortion in 1950 The placenta, umbilical cord and fetal membranes were not remarkable

Postmortem examination The infant was a male, externally well-formed and normally proportioned, 38 cm long and weighed 1660 gm The facial expression was not unusual The thoracic cavity and contents were normal Although the thymus was large (12 5 gm), it was limited to the mediastinum The liver, spleen, pancreas, gastro intestinal tract and biliary passages were normally developed Meconium was present in the entire colon and around the gaping anus

The adrenal glands were disc shaped, and histologically normal Small, well formed testes with attached epididymides were found in the lateral pelvis near the inguinal canals Both kidneys and ureters were absent The unexpanded urinary bladder showed the usual relation with the urachus, umbilical arteries, prostate, seminal vesicles and urethra The penis was well developed The skeletal system was normal

Microscopic studies There was marked congestion and fresh, focal, interstitial hemorrhage in all the tissues, especially in the lung sections Renal parenchyma was not found The tissue of the prostate, urinary bladder, urethra and penis were normal Sections of the pancreas demonstrated comparatively few small islets of Langerhans The thymus and gonads were histologically normal

Case 3 (N 51-216) a 1280 gm , living, male infant was delivered 2 months prior to the calculated term Parents and one sibling were in good health The cyanotic infant (Rh positive, Coombs test on cord blood, negative) displayed "obstructive type breathing" from time of birth, although the respiratory tract was patent. Cardiac function ceased three and one half hours following birth.

The 39.5 cm. long body demonstrated multiple external malformations. There were acromegalic features as manifested by a comparatively large face; oversized jaws, chin and ears; long thin extremities with large hands and feet; and particularly long fingers and toes. The eyes bulged outward from well formed orbits; conjunctival vessels were congested; and the accessory canthal folds were not present. The perineum presented a gaping anus and empty scrotal folds. A broadened penis terminated in a congested glans without the external meatus or prepuce.

Dissection of the head disclosed complete absence of the fontanelles. The meningeal and cerebral vessels were congested with purplish blood but anatomically normal. The well formed brain (210 gm.) contained normal ventricles and choroid plexus but the pituitary was considerably softened and measured 0.5 by 0.4 cm.

All the tissues of the neck and chest were congested and dilated. Although the isthmus of the thyroid was absent, the lateral lobes were enlarged. The four lobed, butterfly shaped thymus (15 gm.) ascended from the mediastinum into the anterior triangle of the neck.

Peritoneal cavity and organs including the pancreas, aorta and ovoid shaped adrenals were normal. Anterior to the meconium filled rectum the bladder was unexpanded and elongated with the attached normal prostatic gland and urethra. A single ureteral orifice was found in the bladder, which was continuous with a one cm. segment of a ductlike structure. The kidneys and ureters were not developed (with the exception of the above). Sections of the penis disclosed partial absence of the urethra. The gonads were located near the inguinal canals.

Microscopic studies of the representative tissue confirmed the normal architecture of most organs. Pituitary gland was composed of approximately 50 per cent acidophilic epithelial cells. There was considerable colloid present in the lumen of the dilated acini of the thyroid gland without evidence of epithelial hyperplasia. The adrenal cortical cells showed a moderate amount of hyperplasia. Throughout the pancreas there was some reduction of the islets of Langerhans.

Multiple sections through the penis demonstrated the two corpora cavernosa. Between the corpora there was a compressed tubular structure lined by pseudostratified, columnar epithelium containing many mucus glands. The glans penis did not contain this structure.

Case 4. (N-50-215) a three pound baby boy, born 6 weeks prior to the calculated term, had respiratory difficulties and intermittent apnea at birth. The pregnancy (mother 21 year old para 1) had been uneventful. The placenta, fetal membranes and umbilical cord were normal. In spite of oxygen the infant remained cyanotic. Urine was not observed at anytime. Meconium passed repeatedly followed by pasty stools. On the fifth day of life blood tinged vomitus was noted. Complete blood count was normal. A flat film of the abdomen was not helpful. On the following day intramuscular pyelography failed to reveal kidney shadows or concentration of the dye Urea nitrogen (micro method) was 87 mg per cent The infant made very few spontaneous motions and there were no convulsions Increasing frequent vomiting and severe cyanosis preceded the cardiac arrest on October 27, 1950

The body weighed 1480 gm and measured 42 cm External malformations were not evident and facial expression was not unusual The scrotum was empty and penis was normal including prepuce and meatus A stricture of the urethra was found near the membranous part

The thoracic cavity including the heart, lungs and great vessels were not abnormal Although the thymus gland was small (2 5 gm) its histology was normal Peritoneal contents were not unusual The left gonad was in the inguinal canal and the right gonad was in the pelvis Pancreas and adrenals were not remarkable There was no evidence of renal parenchyma, pelves or ureters The unexpanded urinary bladder was elongated and contained the trigone but the ureteral orifices were absent Prostate was normal

Additional microscopic findings were acute pneumonitis, slight fatty change of the liver and passive hyperemia of all tissues All endocrine glands were histologically normal Except for undifferentiated epithelial cells in the membranous urethra the penile and prostatic portions were normally developed

CONCLUSIONS

Four new cases of bilateral renal agenesis are added to the literature

Associated clinical and pathological findings are presented, which include various endocrine dysplasias Further studies may reveal definite relationship

The typical "facial characteristics" of renal agenesis, as reported in the literature, have not been corroborated

Clinical observations in our series suggested that persistent gray, cyanotic appearance of an adequately oxygenated infant associated with "obstructive type respirations" can be caused by pulmonary dysfunction secondary to bilateral renal agenesis

The function of the renal parenchyma can be temporarily substituted by other organs in the neonatal period, as demonstrated by case 4, who lived for 10 days

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HISTOLOGICAL EXAMINATION OF THE REGENERATION OF THE URETER IN DOGS AFTER INTUBATED URETEROTOMY

KJÆLD TRAUTNER AND FLEMMING RAASCHOU

From the Department of Surgery, Kommunehospitalet, the Department of Clinical Medicine, Kommunehospitalet, and from the Pathological Institute, Kommunehospitalet, Copenhagen

As a result of the treatment of ureteral strictures in human beings by intubated ureterotomy (by the method invented by Davis), the problem has arisen whether the ureter is capable of regeneration and, if so, to what extent. In order to elucidate the question, the ureters of 7 dogs have been examined histologically at various intervals after partial resection of the ureter and subsequent ureteral intubation.

PREVIOUS INVESTIGATIONS

In 1948 Davis, Strong, and Drake resected in 6 dogs a portion of the ureter representing two thirds of its circumference and about 3 cm. long. The corresponding kidney was removed and the ureter was intubated; at intervals varying from 4 days to 6 weeks the site of operation was examined. Active proliferation of the epithelium was manifest as early as 4 days after the operation; after 3 weeks' epithelialization was complete, the muscular coat occupied about 50 per cent of the circumference of the ureter; after 5 weeks and 2 days the muscular coat occupied 75 per cent of the circumference, and after 6 weeks, 90 per cent.

In 1950 Kimbrough, Furst, David, Worgan, and Denslow made similar experiments on 4 dogs without, however, removing the corresponding kidney, but removing the tube after 8 to 12 weeks; the histological examination was made 2 to 8 weeks later. These experiments were accompanied by so many complications (hydronephroses, development of calculi, angulations, and inflammation), and the histological findings were so scarce that they contributed nothing to the solution of the problem proper, i.e. the regeneration of the ureter.

Herdman (1949) introduced polyethelene tubes in ureters of 15 rabbits; the tubes became soon obstructed by urinary sediments, and the invariable consequence was hydronephrosis, for which reason the author concluded that polyethelene tubes were not fit for ureteral intubation.

In recent experiments on dogs by Blum and Winisdoerffer polyethelene tubes were also introduced into the ureters. In most cases a dilatation of the renal pelvis and the calyx occurred, but no calculi developed. No histological examination of the regenerated ureteral wall was published.

As the research work in Davis, Strong, and Drake's otherwise excellent experiments was carried out under conditions different to those prevailing in cases of ureter regenerations in patients (i.e. the removal of the corresponding kidney) we have felt the need to repeat the experiments under more satisfactory physiological conditions. The corresponding kidney has not been removed in our experiments.

This work was supported by grants from the King Christian X Fund, and from the P. Carl Petersen Fund.

TECHNIQUE

Seven medium size dogs of about one to two years old were used Under intravenous nembutal anesthesia a transperitoneal, and usually a longitudinal pararectal, incision was made After mobilizing the ureter, a portion of the latter representing two thirds of its circumference and of a length of 3 to 8 cm was removed A polyethelene tube of suitable size was then introduced 3 to 5 cm proximally and distally to the site of the ureterotomy The remaining ureteral segment was then fixed round the tube by 3 to 5 silk sutures To obviate angulations the intubated ureter was usually secured towards the posterior abdominal wall In 2 cases the polyethelene tube was inserted as far down as into the bladder, and in 2 cases it was taken through the renal pelvis and brought out through a nephrostomy, with a view to later removal of the tube the upper closed end was secured subcutaneously Only in 1 dog (No 6) was the tube removed (27 days) after intubation The animals were sacrificed or died at periods varying from 4 to 77 days after the operation, the urogenital organs were dissected, and the site of ureterotomy examined histologically in transverse section Hematoxylene eosin and Van Gieson Hansen stains were used

The mean blood pressure (gauged by a mercury manometer in the femoral artery) and the blood urea of the dogs were checked both before and after the operation, in some cases the renal function was also checked (endogenous creatinine clearance, urea clearance, and PAH clearance)

The polyethelene has proved suitable as a tube material causing no development of calculi The rigidity is the only drawback of the material since it may give rise to angulations of the ureter at the tube ends

FINDINGS

As already mentioned the experiments were performed on 7 dogs but the total number of operations amounted to nine, as in 2 dogs the operation was performed on either ureter The dogs were examined 4, 6, 10, 13, 19, 27, 50, 59, and 77 days after operation, as is shown in table 1

Two out of the nine ureterotomies later examined revealed no complications, but in the other cases complications were numerous The most frequent occurrence was a varying degree of hydronephrosis (6 cases) either as a consequence of angulation (2 cases) or because the tube had penetrated too far into the renal pelvis (2 cases), in 1 case (dog No 5, left side) in which the tube was discharged spontaneously during lifetime, the hydronephrosis may have developed because the tube had become fixed in the pelvis In 1 case (dog No 4) the tube had moved half-way out of the ureter towards the urethra In 1 case (dog No 6) in which the catheter was removed during lifetime after 27 days, the post mortem examination, which was performed 50 days postoperatively, disclosed a severe inflammatory stricture at the site of resection, collaterally, severe pyonephrosis and purulent peritonitis had developed Among other complications cases of ossification at the site of resection may be mentioned (2 cases), slight hypertension (2 cases, both combined with hydronephrosis) and one reflex anuria (1 case), besides, in 2 dogs (Nos 5 [right side] and 7) a peculiar develop-

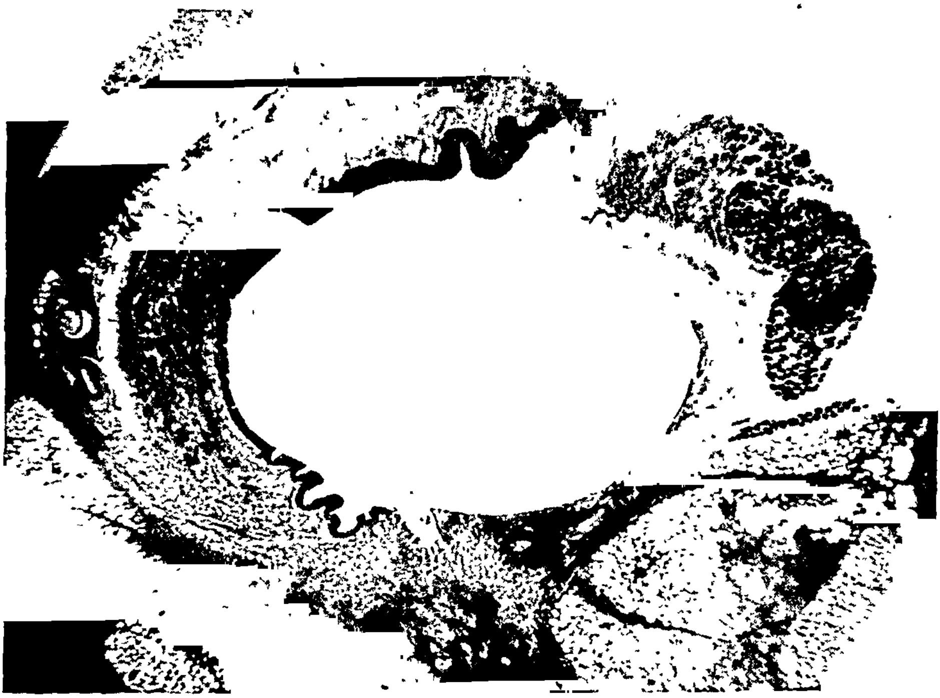

FIG. 1. Dog No. 2. Site of resection. Right ureter.

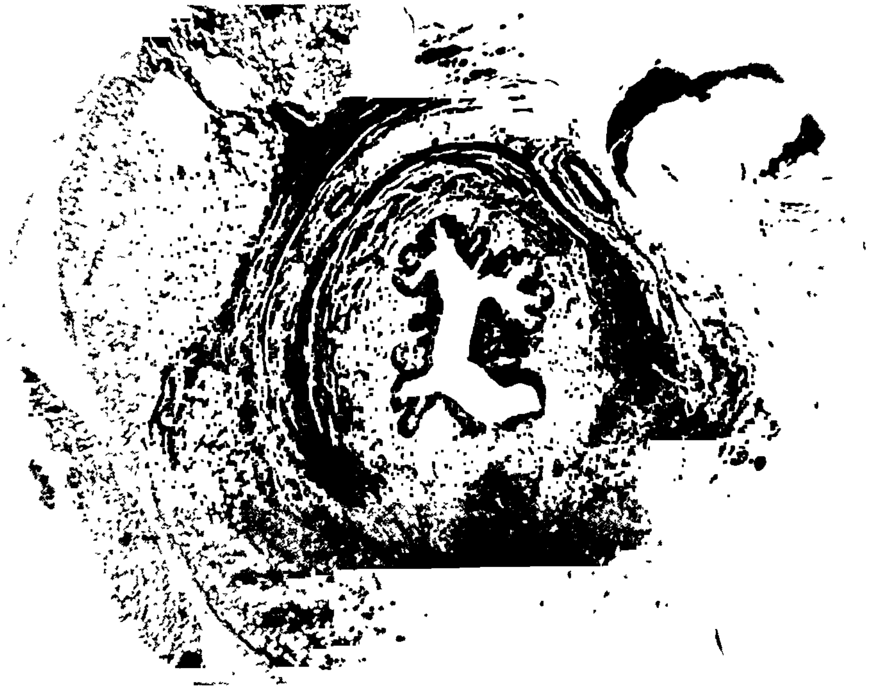

FIG. 2. Dog No. 2. Site of resection. Left ureter. Low power view.

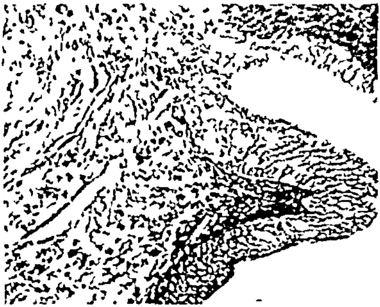

FIG 3 Dog No 2 Site of resection Left ureter High power view

tions from the site of resection showed normal epithelium covering the entire surface Otherwise the ureter was composed of normal ureter wall components corresponding to more than two thirds of the circumference (including circular as well as longitudinal muscles), the remaining one third was composed of mainly unorganized new connective tissue covered by epithelium The boundaries between the two sections were indistinct High power view of the latter section (fig 3) showed the wall to be composed of connective tissue covered by epithelium The epithelium was normal

Dog No 3 A portion of the left ureter representing two thirds of its circumference and of a length of 4 to 5 cm was removed A polyethelene tube was introduced into the ureter During the ensuing 10 days the blood pressure and the blood urea remained normal Ten days after the operation a post mortem examination was performed

Postmortem examination There was no angulation of the left ureter and no dilatation of the left pelvis The site of the ureterotomy was coiled in adhesions and was the site of slight peri ureteric thickenings The polyethelene tube was in place Figure 4 shows a gross specimen (transverse section) of the left ureter corresponding to the site of resection it will be seen how a massive tube of tissue has developed round the polyethelene tube already on the tenth day

Histological examination, 10 days, low power view, Van Gieson-Hansen stains (fig 5) Sections from the site of resection showed the entire circumference covered by epithelium However, in part of the ureter wall it had loosened (Under the high power view scattered remnants of epithelium were observed) Otherwise the composition of the wall was as follows a) one sixth of the wall was normal, and b) in the remainder, circular muscle was present but was interrupted in two places where the wall was composed of connective tissue exclusively This section contained no longitudinal muscle and the layers of circular muscle were pronouncedly thinner than in the original ureteral wall There was, however, much cellular connective tissue, in the submucosa as well as outside the muscle

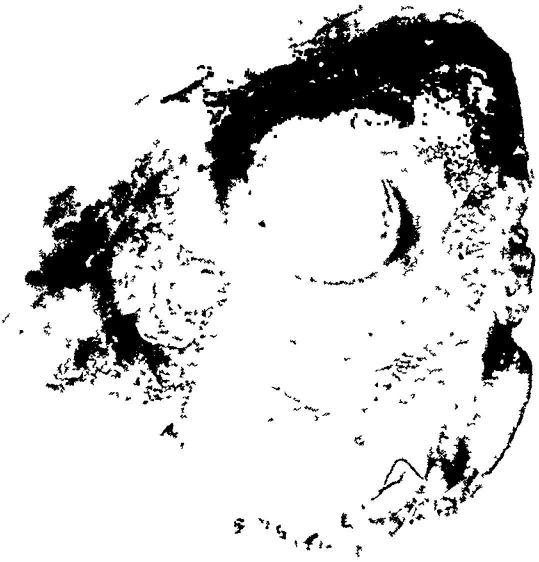

FIG. 4. Dog No. 3 Gross specimen Transverse section of left ureter corresponding to site of resection.

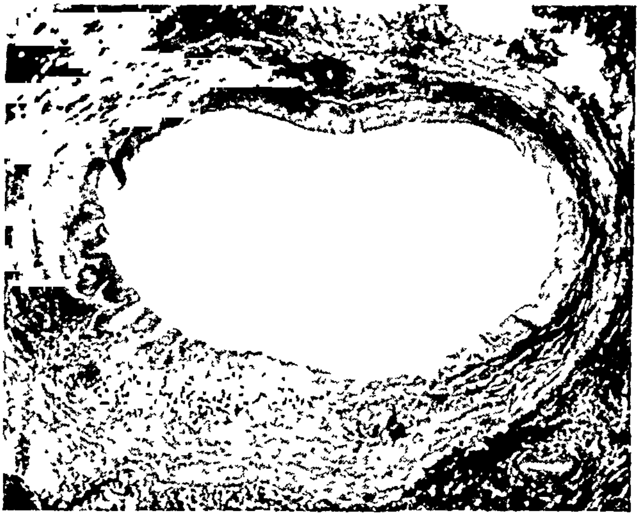

FIG. 5 Dog No. 3 Site of resection Left ureter Low power view.

This is a case of rapid regeneration of the circular muscle in almost the entire area of regeneration. Epithelium is covering the entire surface, even the two small sections where the wall is composed of connective tissue exclusively.

The high power view (fig. 6) shows one section of the wall covered by epithelium but with no muscle, and the wall is composed of connective tissue exclusively.

Dog No. 4. Autolysis rendered the tissues of this animal useless for histology.

Dog No. 5. Four centimeters at about the center of the right ureter were removed leaving nothing but a narrow dorsal ribbon of the ureter. A polyethelene

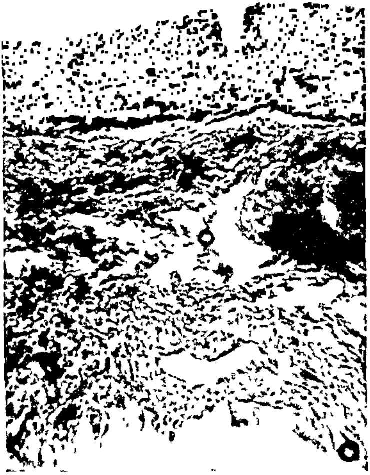

FIG. 6. Dog No. 3. Site of resection High power view

tube was introduced into the right ureter penetrating into the right renal pelvis and 4 cm. below the site of resection. Fifty days later the left ureter was opened at a length of 3 cm. and a polyethelene tube was introduced.

Previous to the first operation the renal function was as follows: Urea clearance: 106 ml. and 82 ml. Endogenous creatinine clearance: 92 ml. and 103 ml. Para-amino-hippuric acid clearance: 438 ml. Eight days after the first operation the renal function was as follows: Urea clearance: 28 ml. Endogenous creatinine clearance: 47 ml. Para-aminohippuric acid clearance: 148 ml. It will be observed that the renal function had gone down to one third of the original value.

The general condition was satisfactory throughout. Urination was normal after the first operation. During the first 9 days after the second operation, hematuria was observed in macroscopic examination. Five days after the second operation (fig. 7) the concentration of blood urea increased from 40 to 50 mg. per cent up to 219 mg. per cent (11 days postoperative). During the following days the blood urea went down again, probably on account of the spontaneous discharge of the polyethelene tube from the left ureter which was disclosed at the subsequent postmortem examination. At the postmortem examination (27 days after the second operation) the blood urea had gone down to 69 mg. per cent. The mean blood pressure (fig. 7) was tested daily from 54 days before the first operation until the post mortem examination.

Even after the first operation a slight increase in the blood pressure appeared, which continued after the second operation. The total increase was about 25 mm. Hg, and was probably due to the bilateral hydronephrosis which was disclosed at the post mortem examination.

Postmortem examination was made 27 days after the operation on the left ure-

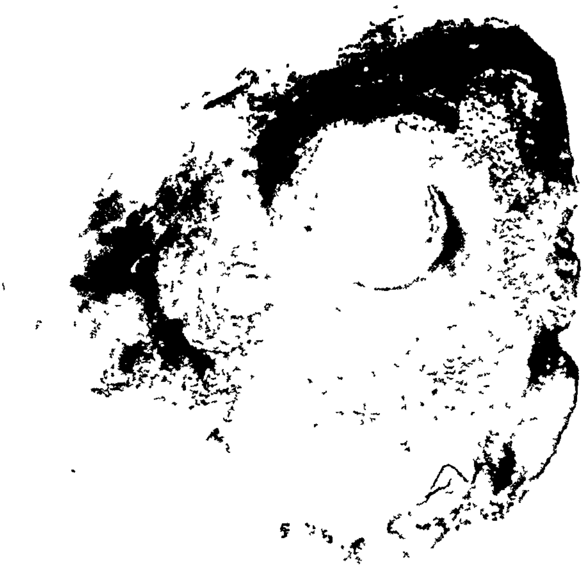

FIG. 4. Dog No. 3. Gross specimen. Transverse section of left ureter corresponding to site of resection.

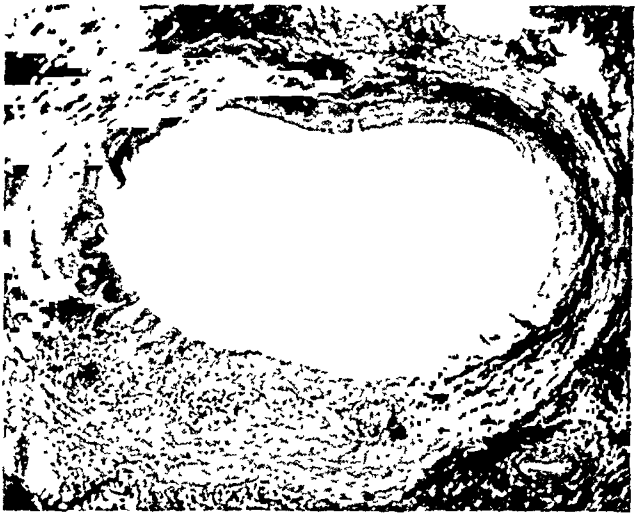

FIG. 5. Dog No. 3. Site of resection. Left ureter. Low power view.

This is a case of rapid regeneration of the circular muscle in almost the entire area of regeneration. Epithelium is covering the entire surface, even the two small sections where the wall is composed of connective tissue exclusively.

The high power view (fig. 6) shows one section of the wall covered by epithelium but with no muscle, and the wall is composed of connective tissue exclusively.

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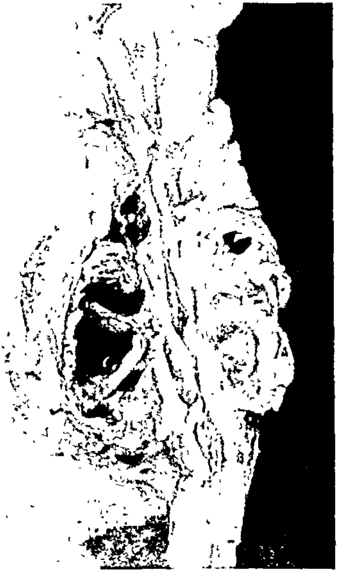

FIG. 8. Dog No. 5. Site of resection. Right ureter. High power view.

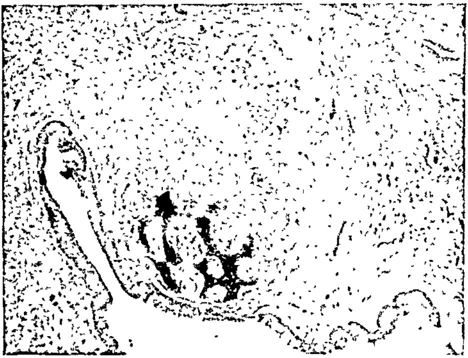

FIG. 9. Dog No. 5. Site of resection. Left ureter (dissected).

Dog. No. 6. A portion of the left ureter representing two thirds of its circumference and of a length of 5 cm. was removed. A polyethelene tube was introduced and brought out through a left nephrostomy; the tube was secured in the muscles of the left loin. The part of the tube which was situated in the renal pelvis was provided with fenestrae. Twenty-seven days after the operation the tube was removed through an incision in the left loin. For a period the dog was well and urinated freely, but gradually it declined, and 50 days after the first operation the dog was killed in nembutal anesthesia.

Postmortem examination disclosed a pronounced left pyonephrosis due to an inflammatory ureteral stricture at the site of resection. A severe purulent peritonitis was also present.

Dog No. 7. A portion of the left ureter representing about three fourths to four fifths of its circumference and of a length of 7 cm. was removed. The dog was observed for 59 days; the general appearance was satisfactory, but a slight increase in the mean blood pressure occurred (from about 135 mm. Hg to about 170 mm. Hg). The renal function remained stable. Fifty-nine days after the operation a left ureteronephrectomy was performed which was followed by a moderate fall in the blood pressure.

Sections from the operative site, including the left kidney and ureter, revealed pronounced hydronephrosis and total atrophy of the renal parenchyma. The upper 3 to 4 cm. of the left ureter were dilated because of an angulation proximal to the polyethelene tube. The site of the ureterotomy was heavily thickened at a length of 4 to 5 cm. A horizontal section of the site revealed a smaller circular lumen (the regenerated ureter) and next to it a greater lumen corresponding to a new chamber, covered by epithelium, of a length of 1½ cm., which was close to the ureter.

Histological examination, 59 days, low power view, Van Gieson-Hansen stains) (fig. 10): Sections from the site of resection (that the proper site has been found is proved by the suture material revealed in high power view) showed that four fifths of the circumference was formed by the original ureter wall; in places both the epithelium and the muscles were defective. The remaining

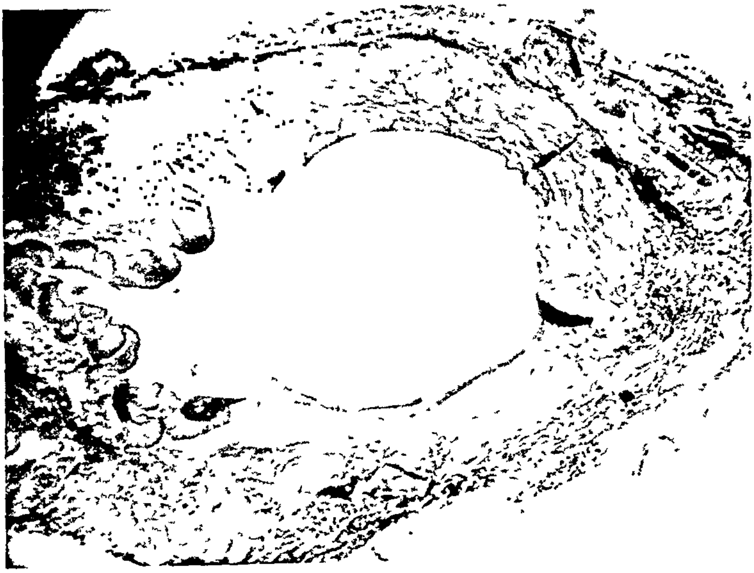

FIG. 10. Dog No. 7. Site of resection. Left ureter.

one fifth was composed of connective tissue interspersed by moderate amounts of isolated muscle tissue and covered by rather high epithelium

DISCUSSION

The object of our experiments has been the histological examination of the regeneration of the ureter wall in dogs in whom a portion of the ureter wall representing two thirds of its circumference and of a length of 3 to 8 cm has been removed followed by the introduction of polyethelene tubes (but without the removal of the corresponding kidney) The findings were as follows

1) The regeneration of the epithelium is rapid, and already 10 days after the operation epithelium covers the entire defect

2) Primarily, the ureteral defect will be replaced by connective tissue, and

3) even the muscles are capable of regeneration, in the circular muscle the process of regeneration is rapid, and as early as ten days after the operation almost unintermitted layers of circular muscle were present In sections from the thirteenth day after operation it is found that the circular as well as the longitudinal muscle cover about two thirds of the circumference of the ureter

We have thus been able to confirm the results of Davis, Strong, and Drake In so far as it is possible to apply the results from experiments on healthy dogs to patients treated with ureterotomy by the method invented by Davis, it is justifiable to say that the consequence of the operation is not the development of fistulas or scars corresponding to the original stricture, but the regeneration of the ureter wall

In addition it has been shown that polyethelene tubing is a suitable material for intubation, a fact of importance in clinical surgery Clearly the occurrence of calculi is obviated by this method

SUMMARY

The object of the experiments has been to examine in dogs whether the ureter will regenerate after partial resection, followed by introduction of polyethelene tubes and, if so, how the regeneration is effected

Nine ureterotomies have been performed on 7 dogs in which a portion of the ureter representing two thirds of its circumference and of a length of 3 to 8 cm has been removed Polyethelene tubes were introduced into the ureters, but the corresponding kidney was not removed Histological examinations of the areas of resection were made at intervals varying from 4 to 77 days after the operation, and the findings were

The ureteral epithelium will regenerate rapidly, as early as 10 days after the operation, the entire defect is covered by epithelium

Primarily, the ureteral defect is replaced by connective tissue

Afterwards there is regeneration of the muscles There is an almost continuous layer of circular muscle, and a little later the regeneration of the longitudinal muscle occurs

It thus appears that polyethelene is a very suitable material for tubes as it produces no development of calculi

Intubated ureterotomies on dogs have, however, been hampered by many complications: ureteral angulations, shiftings of the tubes, hydronephroses, pyonephrosis, ossifications, hypertension, and possibly reflex anuria, and if previous experience did not show that complications in human beings are much less frequent, the application of this method to man would have been impossible.

The authors gratefully acknowledge the technical assistance of Miss Kirsten Berrig, Miss Xenia Boysen, Mrs. Anna Jørgensen and the medical students Marius Carl, Helge Olsen and Uve Petersen.

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TIDAL DRAINAGE OF THE URINARY BLADDER

WILLIAM F McKENNA

Tidal drainage of the urinary bladder can be defined as the rhythmic, artificial, slow filling, and rapid emptying of the bladder in as nearly a physiological manner as possible

The first description of the procedure in this country was offered by Munro in 1935 His demonstration and the apparatus he employed were based on studies concerning the irrigation of the pleura, the bladder, and other hollow viscera The basic principles which Munro adopted were presented by Laver in Great Britain in 1917 Since Munro's first paper in 1935 a large number of devices have been suggested, practically all modifications of Munro's Each of these sought to correct some difficulty in making the original model operate successfully, and some were proposed for secondary purposes such as simultaneous cystometry, re irrigation of the apparatus to lessen contamination, measurement of the amount of fluid used, and adaptations to permit the use of two- and three way catheters None of these objectives has any bearing on the fundamental function of tidal drainage, and all of them can be accomplished by simpler and more direct measures than those recommended by the several authors

Every one of the devices presented depends on the action of a syphon for its effect All have an external source of supply for irrigating solution All have an air vent in some portion of the system Otherwise they may be divided into two groups—those that have, in addition to the foregoing, some form of reservoir, and those without a reservoir A full understanding of the method of action of all tidal drainage apparatus requires a brief review of elementary physics, with particular reference to the action of the syphon under varying conditions

Figure 1 shows a container, C (the reservoir), tightly closed by a cork B, which admits A, from the supply source, and S' which is the proximal arm of a syphon $S'S$ Except for A and $S'S$ this is a completely closed system Fluid entering C through A will fill C, and will rise in S' until it reaches the arch of the syphon, when it flows into S Since the negative pressure developed by $S'S$ has no replacement except through A, $S'S$ will only draw off as much fluid as enters through A, and C will not empty, if all joints are tight In this arrangement there can be no syphon action of sufficient moment to empty C

Figure 2 shows the addition of E, an air vent passing through B Fluid now entering C through A will fill C and will then rise in both E and S' When the fluid level in E and S' is sufficiently high, there is an overflow into S, and $S'S$ will empty C and E It is necessary at this point to consider three possibilities, which are very simple and elementary

First The amount of air drawn into the system through E may be very small, and the amount of fluid entering through A may be the same as the capacity of $S'S$ Under this condition $S'S$ will not draw over enough air at any one

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moment to break the syphon, and a mixture of air and water will continue to flow through *S′S*, and *C* will not fill again.

Second: The amount of fluid and the amount of air may be equal, and together be greater than the capacity of *S′S*. Again insufficient air will enter through *E* to fill *S′*, and the syphon action will continue without letting *C* fill again.

Third: The amount of fluid and the amount of air entering through *E* and *A* together will be less than the capacity of *S′*, and *S′* will pull in air enough to permit the syphon to break, and *C* will then fill again. It is only when this third condition obtains in any tidal drainage device that the continued recurrence of the interruption of syphon action is assured.

The foregoing may be summarized in a sort of formula where *R* is rate, and *V* is volume for all three parts of any such system.

RVA is greater than *RVE*, and both together are greater than *RVS′*. The syphon will not break. *C* will not refill.

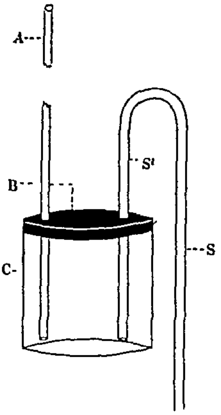

FIG. 1

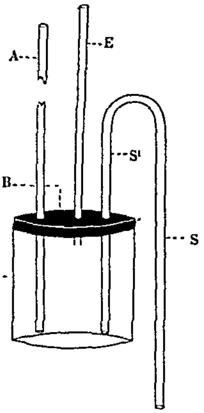

FIG. 2

RVA equals *RVE* and together both are greater than *RVS′*. The syphon will not break. *C* will not refill.

RVA plus *RVE* are together less than *RVS′*. The syphon will break. *C* will refill. Perhaps an apology is due the reader for emphasizing such elementary principles. However, failure to appreciate these facts has been an obstacle to the wider use of tidal drainage.

In figure 3, *A′* is a T-tube inserted in *A* outside of *C*. *A′* is connected to *V* which represents the bladder. Fluid running through *A* into *C* will fill it, and will rise in *A*, *E*, and *S′* to the level of *A′*, at which point it will run into *V*. When *V* is filled to initial stress capacity the fluid will continue to rise in *S′*, and overflow into *S*. *S′S* will then empty *C*, and the contents of *V* will drop into *C* by gravity, and be drawn off by *S′S*. *V* will collapse rapidly, but its collapse will be cushioned by the contents of *C*. *RVA* plus *RVE* must be less than *RVS′S*. There will be no negative pressure, or suction applied to *V*, as this will be dissipated through *C* and its openings.

In figure 4 the same effect is obtained if *S′* be connected by *A′* to *A*. This merely combines *S′* with *A*, and in no way interferes with the total action.

In view of the foregoing it is obvious that the reservoir serves a useful purpose. First, it acts to prime the pump as one might put it. It also acts as a cushion to the emptying of *V*, permitting *V* to empty more by gravity than by the application of negative pressure, which might injure the bladder wall, if excessive. It also acts to minimize the amount of air entering *V*.

Many devices have been described which use only the syphon, T-tubes, and an air vent, omitting the reservoir. Under favorable conditions these will operate, but it must be emphasized that all of them permit almost as much air to enter the bladder, as they do fluid. The formula expressed above must be borne in mind when using any of the devices of this type. In many, the T-tube is displaced by a Y-tube, but the structural difference is of small moment. Air will enter *V* up to the point at which *V* begins to distend, which is usually about 50 per cent of its capacity, more or less, depending on the degree of paralysis. From this point on the fluid levels in *A*, *E*, and *S'* will rise, until *S'S* acts, allowing *V* to empty. The flow from *A* is still going on, and after the first emptying cycle has been completed, this flow from *A* may continue to pass over through *S'S*

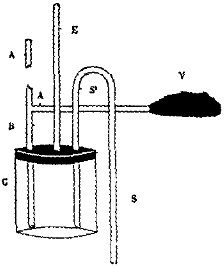

FIG. 3

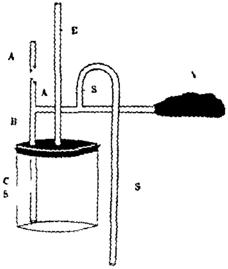

FIG. 4

unless it is limited to a very slow rate. This type of device may be modified by adding other T- and Y tubes to provide openings for manometry readings, while the irrigating cycles are in progress. A closed drip in the supply line may be compensated for by an extra T-tube. All of these extra parts add complicating accessories to a system which is at best imperfect. In some recommended hook-ups, the air inlet is a small hypodermic needle inserted into some part of *A*, and the dropper is a closed one. Figure 5 shows the general construction of such a system, where *W* signifies a manometer attachment, and where *E* may be an added air inlet.

Figure 6 illustrates a single, compact unit which requires no extra parts. A careful study will show that it has all the essential features of a tidal drainage instrument as is shown in figures 1–4. It can be readily sterilized, either by boiling or in the autoclave, as it is made entirely of Pyrex glass. It is a considerable improvement over the unit described by the author in 1948, as it is smaller and therefore uses less irrigating fluid in each drainage cycle, as its effective capacity is about 25 cc. The rate of flow is always visible and can be controlled as in other assemblies, by a clamp above the unit to regulate the supply. In addition, *E* is not only an air vent in this unit, but is a safety overflow should the catheter become plugged.

It is generally accepted that 10 cm. of water pressure is the level at which the bladder registers any sensation of contents. This does not induce a desire to void which develops at varying pressures up to 50 to 80 cm. water pressure, which is about the maximum of tolerance. It seems a safe level for any intact bladder, and the unit shown is designed to operate at maximum efficiency at pressures up to 10 cm. water. It is well to carry in mind the fact that mercury readings are about one tenth of water readings, since mercury is a little more than ten times as heavy as water. From considerable experience, 10 cm. water pressure is generally a safe level in the totally paralysed bladder, provided it has not been weakened by too long overdistention or advanced infection. The apparatus will work at lower pressures equally well. In setting up the unit the outlet to the bladder, *A′* should be at the level of the base of the patient's bladder, or about even with the rectum. The rate of flow is adjustable between 40 and 100 drops per minute. This will result in irrigating cycles of one to two hours, depending on the capacity of the bladder.

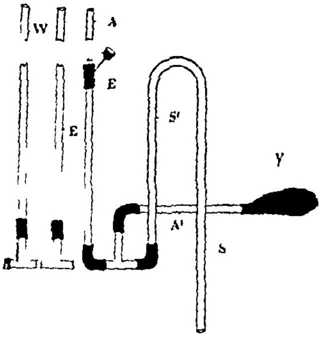

FIG. 5

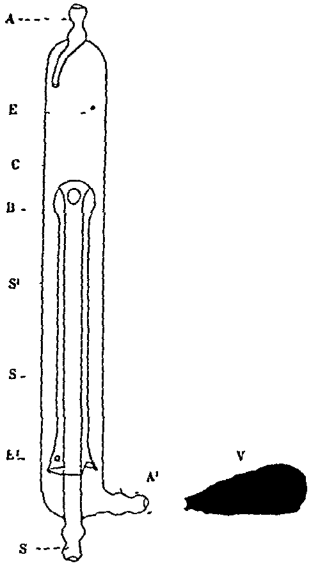

FIG. 6

When it is felt that the pressure on the bladder should be less than 10 cm. water, the unit can be lowered. The container at lower levels will not completely empty, but the bladder will. The amount of fluid remaining in the unit will be in proportion to the distance below the bladder at which the unit is set, and the bladder pressure will be equal to the air space above the fluid level in the unit at the end of the irrigation cycle. In the totally paralysed bladder of transverse myelitis, tidal drainage should be instituted immediately before overdistention ruins the structure of the bladder. By preserving the integrity of the detrusor the period of redevelopment of function is shortened, and the final stage of the uninhibited cord bladder will occur in a shorter time.

Infection is less apt to take place in a bladder which is frequently washed with a suitable antiseptic solution than it is in the overdistended bladder containing a large amount of stagnant urine Patients tolerate an indwelling catheter well if due care is exercised in frequent changing of the catheter, and proper policing of the urethra In this era of antiseptics and antibiotics damage from a permanent catheter can be held to a minimum If there is urethral obstruction of any kind, an indwelling catheter can readily be introduced through a perineal section

In patients where some degree of distention is desired as therapy, in interstitial cystitis for example, the unit may be set at a level above the floor of the bladder Such a setting presupposes that there is conscious control, and that the patient can empty the bladder against such higher pressures The unit will fill the bladder, and the patient uses the detrusor and the accessory muscles of urination to complete the emptying part of the cycle This change to higher than 10 cm can often be of advantage in re educating the paralysed bladder when function is beginning to return

The unit can also be used for cystometry by allowing measured amounts of fluid to enter the bladder while raising the unit at intervals In this manner it is possible to determine a level at which the patient can just empty the bladder through the resistance of the unit as both amount and pressure levels are increased

A review of the basic principles of physics underlying tidal drainage is presented

A new unit is described which is designed to fulfill the basic principles as outlined It is adjustable to varying levels of pressure, quantity, and rate of flow and is therefor adaptable to a broad range of uses It combines in a single unit all of the elements which are necessary for correct tidal drainage

A comprehensive bibliography is appended No attempt has been made to refer in the text to these articles, as none of them is discussed specifically

624 State St , Ogdensburg, N Y

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SUPERNUMERARY URINARY BLADDER AND URETER, SPIRAL DEFORMITY OF THE URETER, URETERAL DIVERTICULUM, HYPOPLASIA OF THE KIDNEY AND BICORNATE UTERUS A CASE REPORT

CARROLL W BOWIE, FRED K GARVEY, WILLIAM H BOYCE AND ELMER E PAUTLER

From the Department of Surgery, Division of Urology, The Bowman Gray School of Medicine of Wake Forest College, Winston Salem, N C

The rare occurrence of supernumerary urinary bladder plus several unusual clinical and anatomical aspects of the following case have prompted this report

On August 8, 1951, a 17 year old girl, N C B No 133421, was admitted to the urological service with the chief complaint of incontinence of urine since birth She voided normally at regular intervals but had to wear a pad during the day because of frequent dribbling of urine in small quantities when she was erect This incontinence was not troublesome when she was lying down and she rarely wet the bed at night Since the age of 3 years she had had intermittent episodes of acute cystitis which had responded promptly to various chemotherapeutic and antibiotic regimens but recurred at intervals of 1 to 3 months Frequent changes of the absorptive pad had permitted her to attend school and to lead a fairly normal life

Physical examination revealed an asthenic young adult girl with blood pressure of 110/78 The external genitalia, vagina, and cervix uteri were those of a normal nulliparous female A slightly tender cystic mass approximately 7 cm in diameter was palpable in the midline anterior to the uterus but no other intrapelvic abnormalities were noted No evidence of an aberrant ureteral orifice could be demonstrated about the vestibule or within the vaginal vault

The complete blood count, blood nonprotein nitrogen, and urinary excretion of phenolsulfonphthalein were within normal limits Urine analysis revealed innumerable white blood cells and bacilli but no casts or albuminuria Culture of the urine was positive for Aerobacter aerogenes and Proteus mirabilis Excretory urograms indicated a normal nephrogram, renal calyces, pelvis and ureter on the left without evidence of excretion from the right kidney In the 45 minute roentgenogram a slight amount of contrast material was present within the lower 5 cm of the right ureter and a spherical density 8 cm in diameter was visible posterior and superior to the cystogram (fig 1, A)

Sensitivity studies indicated that the strain of Proteus mirabilis isolated from the bladder culture was sensitive to chloramphenicol and this was administered in doses totaling 1 0 gm daily After the symptoms of acute cystitis subsided, cystoscopy and urethroscopy revealed a normal urethra and a normal urinary bladder of 500 cc capacity The ureteral orifices were normal in position and appearance but no urine was observed to flow from the right orifice Attempts to catheterize the right ureter met with an obstruction at 3 cm and roentgeno-

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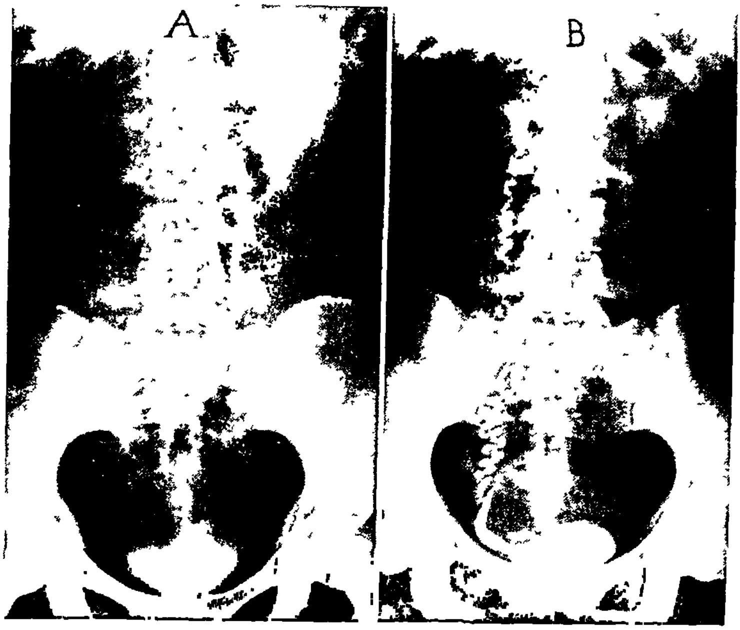


FIG. 1. *A*, forty-five minute excretory urogram. Normal left pyelo-ureterogram without evidence of excretion from right kidney. *Note symmetrical soft tissue density of supernumerary* bladder superimposed upon cystogram of normal bladder. *B*, retrograde injection of bulb catheter wedged in right intramural ureter. Note tortuous right ureter with imperfect filling of right renal pelvis. Pelvic ureter opens into supernumerary bladder which is visible above cystogram produced by reflux of contrast material into true bladder.

grams were made following injection of skiodan through a bulb catheter wedged within the right ureteral orifice. A markedly tortuous ureter was thus demonstrated on the right with imperfect filling of the renal pelvis. At a point 3 cm. from the bladder a bifurcation of the ureter was demonstrated, the mesial division of which seemed to extend into the retrovesical mass (fig. 1, *B*).

Under general anesthesia a right pararectus abdominal incision was made and the inferior angle was extended to the midline by subsequent division of the right rectus muscle. The tortuous right ureter was identified and was found to terminate in a mass of encapsulated renal tissue 4 by 1.5 cm. in size. The renal blood supply was composed of several small arteries of equal caliber which arose from the aorta in the region of the second lumbar vertebra. A diverticulum of the ureter 2.5 cm. in length was found extending toward the midline at a point 3 cm. inferior to the kidney. The spiral ureter was ligated and divided adjacent to the bladder wall. The point of bifurcation of the ureter was identified 3 cm. from the bladder and the mesial segment was traced into the retrovesical mass. The peritoneum was opened and the uterus was found to be bicornate but both ovaries and both fallopian tubes appeared normal. No other intra-abdominal deformities were noted. The pelvic mass was found to lie between the uterus and the bladder and to be covered superiorly by a reflection of the parietal peritoneum. The arterial blood supply appeared to originate from the anterior divisions of both hypogastric arteries, but the largest vessel was from the right. The mass was incised in the midline and identified as a muscular vesicle with a smooth epithelial lining and containing a small quantity of cloudy urine. The

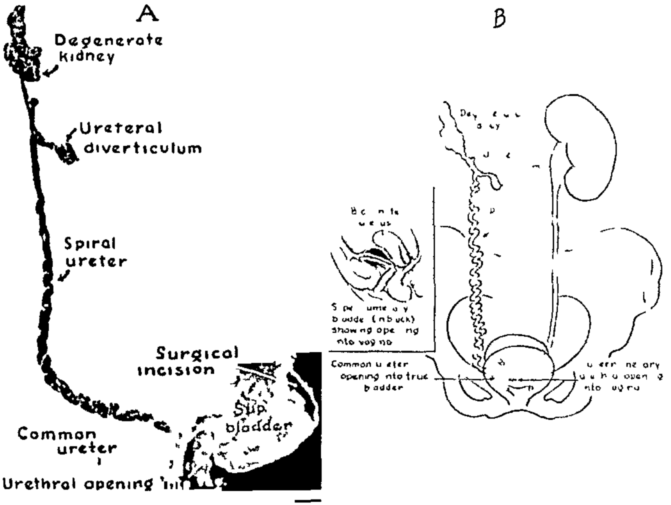


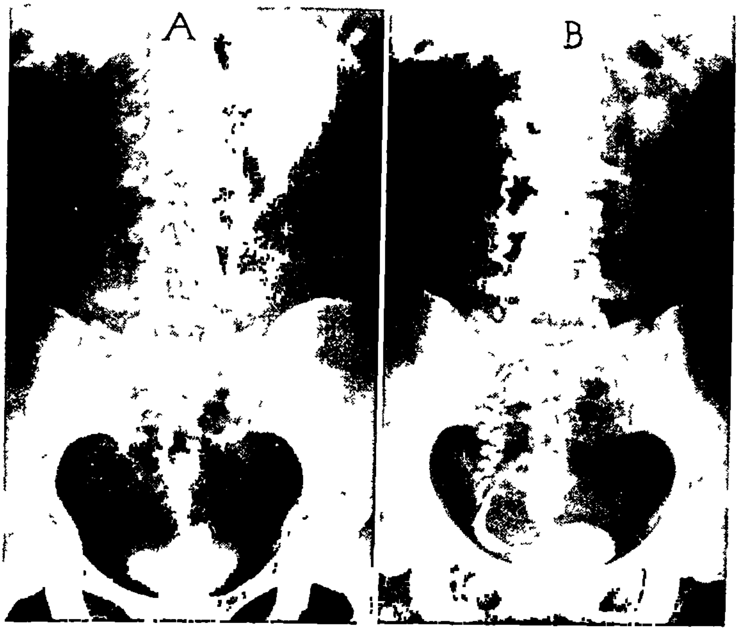
Fig. 2 A, supernumerary urinary bladder and associated structures removed at operation. B, anatomical relationship of supernumerary bladde i Shaded structures were removed at operation. Insert is s to illustrate complete separation of walls of two bladder i s into vagina

mesial segment of the bifid ureter was found to open into this cystic mass by passing obliquely through the muscular wall on the dorsal and inferior surface. A second tubular structure was found to extend from the hollow viscus into the anterior vaginal wall just to the right of the midline. This was ligated and severed flush with the vaginal wall and the specimen removed in entirety (fig 2, A). The anatomical relationships are illustrated in figure 2, B.

The patient made an uncomplicated recovery and has remained entirely continent of urine and free from urinary tract infection until the present time, 16 months postoperatively.

HISTOLOGIC CHARACTERISTICS OF THE TISSUES

The renal mass on cross section seemed to be grossly homogeneous without evidence of cortex or medulla. A few blunt calyces of the first and second order were present but no definite papillae were seen. Histologic examination revealed it to be composed largely of fibro adipose tissue containing many blood vessels, nerves and mononuclear inflammatory cells. Within this stroma numerous discrete foci of spindle shaped mesenchymal cells were observed to be grouped about tubular structures which were lined with simple cuboidal epithelium. Some of these tubules were atrophic but in others the lumina were dilated and contained eosinophilic casts. A few glomeruli which appeared histologically normal were observed.



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Gross and Cresson, 1952, cited the case of Lanman and Mahoney and reported two additional cases which were considered comparable Both of these had exstrophic bladders located on the lower anterior abdominal wall which were entirely separate from the otherwise normal genito urinary systems Therapy consisted of excision of the exstrophic bladders and repair of the defects of the abdominal walls

There have been nine other case reports of complete reduplication of the bladder in which the two vesicles were in close approximation Thus the anomaly appeared to be the result of a complete septum formed between the right and left or between the dorsal and ventral halves of the bladder This septum has been most frequently observed in the midsagittal plane of the body in which case each ureter drained into the homolateral half of the bladder These case reports have been reviewed by Burns, 1947

Union of two ureteral buds to form an inverted "Y" type of ureter is a rare congenital anomaly but the fact that it may occur from ureteral buds arising from the same trigonum would suggest that ureteral buds arising from separated trigonal anlagen may also unite in this manner The dissimilarity of the gross and histologic characteristics of the two ureters supports the supposition that they were of different embryologic origin, that is, the union of two ureteral buds rather than the division of one bud into two ureters

Spiral deformity of the ureter has been reported usually as "torsion" because of the gross appearance This anomaly has been ascribed to rotation of the ureter around the wolffian duct, or as a persistence and rotation of the wolffian duct about the ureter The relationship of this type of ureteral deformity and congenital ureteral valves was noted by Woelfler, 1877, and again by Ostling, 1942 The latter author studied the urinary tracts of 250 fetuses and came to the conclusion that true spiral twist of the ureter does not occur The gross deformity which suggests torsion is in reality serial fold formations which may comprise the whole periphery of the ureter to give the spiral effect The histologic examination of the spiral ureter from the above case report which contained intraluminal folds of mucosa in every "spiral" is in accord with the observations of Ostling Furthermore, since the ureteral and renal anlagen join in embryos of 4 to 6 weeks gestation (8 to 11 mm), it is difficult to explain how a series of 360 degree rotations, which must occur in the ureter prior to union with the kidney, could be evenly distributed along the entire length of the adult ureter (fig 2, *A*)

SUMMARY

A case report has been presented of an adult female who was found to have a degenerate metanephric right kidney with extreme spiral deformity (fold formation) of the associated ureter, and a congenital diverticulum of the upper segment of this ureter A supernumerary bladder was present and drained urine into the vagina through a separate urethra Urine entered the supernumerary bladder by reflux from the normal bladder into the right ureteral orifice which was in communication with the ureter to the degenerate right kidney and with the single ureter from the supernumerary bladder Bicornate uterus was an associated genital anomaly in this patient

Surgical excision of the supernumerary bladder and associated urinary structures relieved the patient of both incontinence of urine and chronic urinary tract infection.

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FOLLOW-UP STUDIES OF BLADDER EXSTROPHY WITH URETEROSIGMOIDOSTOMY

ROBERT A. GARRETT AND JOHN H. O. MERTZ

From the Department of Genito Urinary Surgery, Indiana University Medical Center, Indianapolis, Ind.

Exstrophy of the bladder is said to occur once in every 30,000 to 40,000 births and to be predominantly an anomaly of the male child with reported incidence from 5:1 to 7:1.[1, 2] From July 1941 to July 1952 inclusive, we have operated upon 14 patients with exstrophy of the bladder at Indiana University Medical Center. There have been two operative deaths. One occurred 7 days following ureteral transplantation due to leakage at the site of anastomosis and subsequent peritonitis. The second was experienced during anesthesia induction prior to a proposed ureterosigmoidostomy. This is a mortality rate of 14 per cent, comparing favorably with the experience of others.[1, 2, 3] The 12 patients surviving ureteral transplantation, the basis of this report, with one exception have been followed closely with periodic physical examinations, excretory urography and more recently electrolyte studies.

Much has been published concerning the technique of diversion of the urinary stream into the large bowel. More recently electrolyte aberrations following these procedures have been recognized. However, follow-up studies as just outlined have been scarce. Among the more complete reports are those of C. C. Higgins,[1] Harvard and Thompson,[2] and Hinman Sr.[3]

It is our purpose to present our observations of these twelve patients, realizing the series is small and in some cases the follow-up periods short. We are not attempting to draw conclusions as to the superiority of one method of anastomosis over another, or as to the cause and relationship of the pyelographic and electrolyte changes. Nevertheless, we feel our findings are pertinent as the eventual surgical and medical management of this anomaly will be based upon careful follow-up studies.

MATERIAL

Our series includes 9 boys and 3 girls, a ratio of 3:1. The youngest was 15 months of age, the oldest over thirty-three years. While our intentions have been to operate upon these children at the approximate age of one year, actually most patients have been between 18 months and 3 years of age. Five patients have been followed 5 years or more, eight, 3 years or more, and the remainder 14 months, 9 months, 7 months, and 6 months respectively.

SURGICAL TECHNIQUE

Surgical methods of uretero-intestinal anastomosis used in this series have varied. The Coffey 1[4] operation was utilized in 5 patients, the Jewett[5] technique

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[1] Higgins, C. C.: J. Urol., 63: 852-857, 1950.
[2] Harvard, B. M. and Thompson, G. J.: J. Urol., 65: 223-234, 1951.
[3] Hinman, F.: Calif. Med., 69: 433-434, 1948.
[4] Coffey, R. C.: J.A.M.A., 56: 397, 1911.
[5] Jewett, H. J.: J. Urol., 44: 223-226, 1940.

in three, and the Leadbetter[6] operation in the last four procedures. In 1 child, only the right ureter was transposed, the left demonstrating severe dilatation and infection necessitating nephrectomy. The Leadbetter[6] technique is performed in one stage; the elliptical ends of the ureters are anastomosed directly to the bowel mucosa, the serosa covering this anastomosis to form a tunnel. We implant the ureters as low in the sigmoid as possible, using 5-0 atraumatic chromic catgut sutures.

Preoperative management consists of bowel cleansing with aureomycin and oral streptomycin, with systemic antibiotics when necessary. Low residue diet and cleansing enemas are also utilized. Since the recognition of potential electrolyte changes following this urinary diversion, the patients have been maintained postoperatively on·low salt diets with supplementary sodium bicarbonate.

COMPLICATIONS

Postoperative complications were few in this series. In one patient there was progressive dilatation of the right collecting system due to obstruction at the site of anastomosis, necessitating nephrectomy 4 years after the initial operation. In another patient the ureters were anastomosed by the Jewett technique. Immediate convalescence was uneventful and pyelograms indicated good bilateral function with a grade 2 right hydronephrosis. One month following surgery at the first postoperative visit it was found that the right proximal ureter had re-anastomosed with its distal segment, again draining urine onto the exstrophic bladder! This ureter was again transposed to the colon by the Nesbit procedure. Pyelograms since that time have repeatedly shown reflux of air and contrast media from the colon into the ureter and kidney pelvis.

Following Leadbetter implants in a recently operated patient, progressive abdominal distention with free fluid in the peritoneal cavity was noted on the second post-surgical day. Upon exploration, the left ureter was found to be separated from the bowel, draining urine into the peritoneal cavity. The ureter was re-anastomosed. Convalescence was without further complication and subsequent pyelograms have been normal bilaterally.

Symptoms of pyelonephritis have been noted in six of the 11 patients studied. In one child repeated episodes of right infected hydronephrosis compelled right nephrectomy in 1951. He has had no infection clinically since that event. Despite apparently normal pyelograms, another child has had repeated attacks of fever, chills, and loin pain controlled by antibiotic medication. The child whose severed ureter reunited with the bladder had repeated bouts of right pyelonephritis prior to re-implantation of that ureter. Since that procedure his only complaints have been periodic flank pain with defecation, presumably the result of recto-ureteral reflux. A thirty-three year old female, who had had numerous prolonged episodes of pyelonephritis increasing in duration and severity prior to surgery, had urographic evidence of bilateral pyelonephritis. Curiously enough, since ureterosigmoidostomy her infections have decreased in number and intensity and there has been evidence of urographic improvement of the calycine and pelvic patterns.

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[6] Leadbetter, W. F.: J. Urol., 65: 818–830, 1951.

TABLE 1. *Post-anastomosis urography*

	PELVES		URETERS	
	Number	Per cent	Number	Per cent
No dilatation	17	74	12	52
Grade 1 hydronephrosis	2	9	5	22
Grade 2 hydronephrosis	1	4	3	13
Grade 3 hydronephrosis	2	9	0	0
Non-visualized	1	4	3	13
Total	*23*	*100*	*23*	*100*

Height and weight studies indicate that there has been fundamental disturbance of growth. All children who were operated early in life are found to fall in the lower half of normal or in subnormal groupings, according to the anthropometric chart of Stuart.[7] This deficiency may well be a reflection of repeated infections, either clinical or latent.

PYELOGRAPHY

All patients undergoing ureterosigmoidostomy are subjected to periodic excretory urographic studies. Our usual policy is to make pyelograms at the 1 week, 3 month, 6 month, and 1 year intervals, with subsequent studies annually. In this manner the course of events in ureteropelvic anatomical alteration subsequent to diversion of the urinary stream are recorded. In our study, to facilitate analysis of the pyelograms, we shall refer to the 24 ureteropelvic systems involved rather than to the individual patient. All of the 12 patients studied have had at least two post-surgical pyelographic studies varying from 14 weeks to 11 years postoperative.

Prior to transplantation, it was noted either by retrograde or excretory technique that there were nineteen normal ureteropelvic systems, two pelves showing pyelonephritic changes, and one showing advanced hydronephrosis. In one patient preoperative pyelographic studies were not done, thus accounting for 24 systems in 12 patients. One kidney subsequently was sacrificed without transplantation due to advanced stasis.

Considering the most recent pyelograms of the twenty-three transplanted ureteropelvic systems, seventeen or 74 per cent are considered normal, while six or 26 per cent show some degree of dilatation or erosion not noted prior to surgery. Ureterograms, on the other hand, were found normal in twelve or 52 per cent of the systems, with eight or 35 per cent showing some degree of dilatation, and three or 13 per cent not visualizing sufficiently to warrant opinion (table 1). Further, if pyelographic data are correlated with the various surgical procedures done (table 2), it is interesting to note that four of nine ureters transplanted by the Coffey 1 technique have resulted in normal pyelograms, five of six transplanted by the Jewett technique are normal, and eight of eight transplanted by the Leadbetter technique are normal or better than prior to trans-

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[7] Stuart, H. C.: Am J. Pub Health, 36: 1365–1386, 1946.

TABLE 2. *Pyelography correlated with technique*

TECHNIQUE	NO. OF KIDNEYS	NORMAL	GRADE 1 HYDRO.	GRADE 2 HYDRO.	GRADE 3 HYDRO.	NON-VISUALIZED
Coffey 1	9	4	2	1	1	1
Jewett	6	5	0	0	1	0
Leadbetter	8	8	0	0	0	0
Total	23	17	2	1	2	1

plantation. It should be reasserted that no conclusion can be drawn in this correlative study due to the relatively short follow-up in the group in which the Leadbetter technique was used. Most recent urographic studies are illustrated in figures 1 and 2.

REFLUX

Stimulated by recent work of Baker and Miller,[8] who have shown that reflux of bowel contents into the transplanted ureters is a common finding due at least in part to the extremely high intrarectal pressure during defecation, we have attempted studies in our patients to depict this phenomenon roentgenographically. In our study group, ten of 12 patients were given skiodan enemas sufficient to produce a strong urge to defecate. Abdominal x-ray films were taken synchronous with this urge and again 15 minutes later. In only one ureter was reflux noted, this being the ureteropelvic system in which repeated air pyelo-ureterograms had been found previously. It is our opinion that the incidence of observed reflux would be much higher had these investigations been carried out under fluoroscopy. This piece of work remains to be repeated.

ELECTROLYTE IMBALANCE

Of this group of patients, all but one had at least one electrolyte profile study, nine patients having more than one. An electrolyte profile consisted of determinations of serum sodium, potassium, chloride, and CO_2 combining power. Certain findings in these numerous profiles are felt to be important and are recorded in table 3.

First, every one of 11 patients studied at one time or another carried serum chloride levels in excess of the commonly-accepted upper limits of normal (106 m/Eq. or 375 mg. per cent. In those patients studied more than once, normal levels of serum chloride were occasionally obtained during periods of restricted salt diet. In others normal levels were found without dietary restriction.

Second, eight of the 11 patients studied here at one time or another had a reduction of their alkali reserve as shown by subnormal levels of the CO_2 combining power. In none of these patients found to have a loss of alkali reserve were acidotic symptoms observed clinically.

Third, nine of 11 patients studied displayed definite subnormal levels of serum potassium and the remaining two levels recorded were in the lower limits of normal range. Thus it is safe to say that there was a hypokalemic tendency in all patients studied.

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[8] Baker, R. and Miller, G. H.: J. Urol., 67: 638–643, 1952.

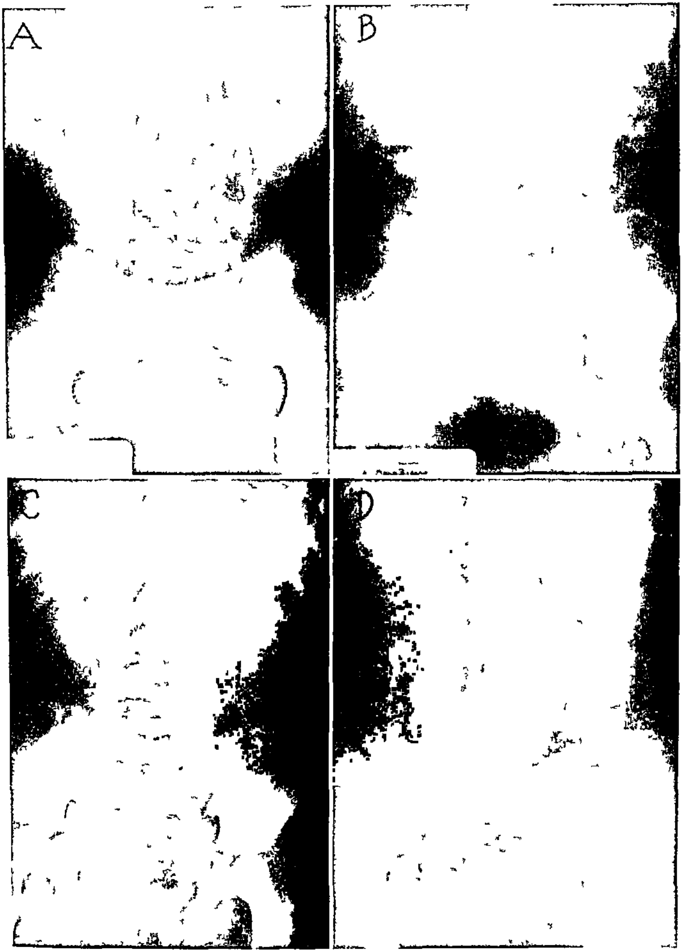

FIG [illegible] 1 two stage completed 1/25/44, aged 10 years Pyelography [illegible] mal left pyelogram Grade 1 hydronephrosis on right, with ur [illegible] 69007 Coffey 1 two stage completed May 23, 1945, aged 2 years Normal bilateral excretory urogr [illegible] ureteral dilatation *C*, J R, No 90787 Jewett operation [illegible] Normal bilateral excretory urograms 10/15/51 *D*, D W [illegible] mpleted 3/5/48, aged 11 years Essentially normal bilateral excretory urograms 7/26/52

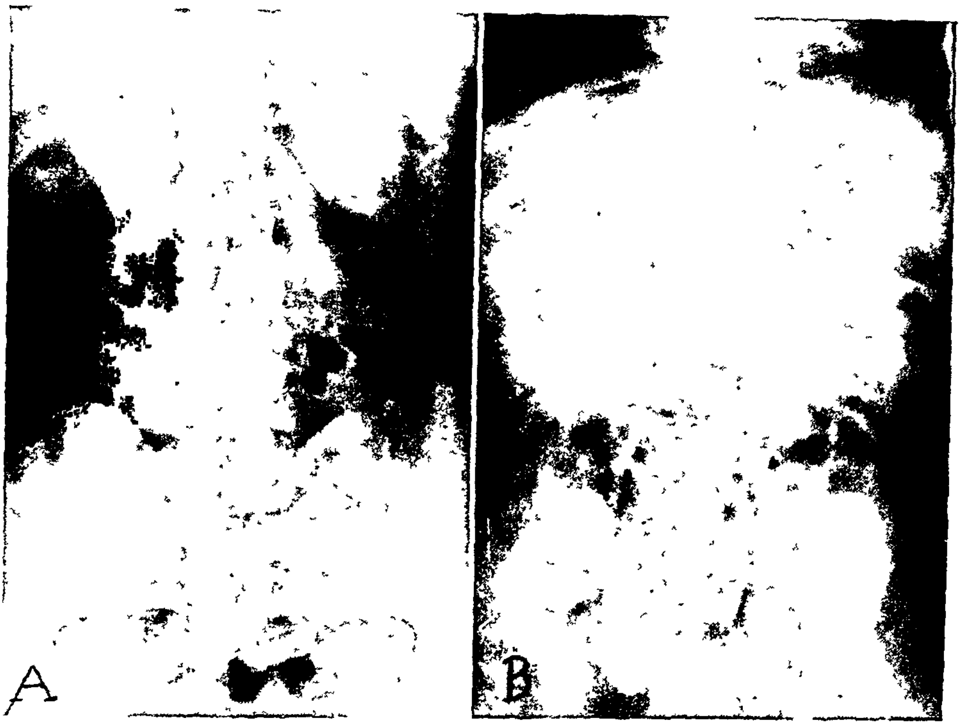

Fig. 2. *A*, B. M., No. 157755. Leadbetter procedure 6/8/51, aged 33 years Excretory urogram, 8/1/52, shows improvement of preoperative pyelonephritic changes. *B*, T. R., No 137936 Leadbetter procedure 4/16/52, aged 2½ years. Normal bilateral excretory urogram 8/5/52.

Table 3. *Electrolyte studies of eleven patients*

	NUMBER	PER CENT
Hyperchloremia	11	100
Alkali reserve reduction	8	73
Hypokalemia	9	82
Hyponatremia	4	36

Fourth, in one patient, where salt restriction alone was used, a definite hyponatremia resulted, apparently corrected on addition of sodium bicarbonate to the diet. In three others hyponatremia occurred without dietary restriction of sodium.

DISCUSSION

Three features of the postureterosigmoidostomy peroid are generally found to contribute to a poor result. These are obstruction, infection, and electrolyte imbalance. In general, infection tends to be mild unless obstruction supervenes, in which case rapid renal destruction may ensue. Electrolyte imbalance may and regularly does occur in the clinical absence of the other two, but tends to be more severe when they are present. The efforts of most interested clinicians are therefore directed toward the elimination of the obstruction and a better understanding of the cause and control of electrolyte imbalance.

With the newer techniques of surgical anastomosis and with painstaking surgical meticulousness, the factor of obstruction is being reduced significantly The application of the mucosa to mucosa principle of Nesbit[9] and Cordonnier,[10] coupled with the tunnelling feature of the Coffey operation, seems to offer much in this regard Our best anatomical results have fallen into this category

The study by pyelography of anatomical changes in the pelvis and ureter is an important feature of follow-up investigation Urography early in the postoperative phase often discloses a *temporary pyelectasis and ureterectasis* These changes are most likely due to edematous constriction at the site of anastomosis Pyelography at the three month interval after anastomosis is more reliable as an index of the integrity of the anastomosis

Reflux, always an important and potential threat, must be reckoned with While we demonstrated this phenomenon only once in our studies, it is possible that it has occurred with greater frequency

Aberrations in the electrolyte composition of the blood was first pointed out by Boyd[11] in 1931 and subsequently by Jewett[12] in 1944 It remained for Ferris and Odel,[13] however, to focus attention on the role of the chloride ion in the *production of acidosis Boyce and Vest[14] have suggested that the chloride ion is* reabsorbed across the rectal mucosal barrier with the ammonium ion, the latter being removed from the blood stream by the liver and converted to urea The excess chloride is neutralized by the plasma alkali reserve and fixed base and excreted as sodium chloride or ammonium chloride The excess urea is likewise excreted and in the bowel or where there is urinary infection it is changed by urea splitting organisms into ammonia making more ammonium chloride available for absorption This ultimately results in a lowering of the alkali reserve and fixed base and an increase in the serum chloride Lapides[15] has proposed that the normal kidney is able to handle this excessive absorption of chlorides and that severe changes in the blood chlorides and alkali reserve are correlated with impairment of renal function D'Agostino[16] has found on colonic perfusate studies that certain electrolyte exchange phenomena occur Perfusates containing 155 *m/Eq of sodium chloride instilled into blind colonic pouches show selective* activity of bowel mucosa to the end that potassium and bicarbonate ions replace significant quantities of sodium and chloride ions independent of osmotic action *It would appear that hyperchloremia follows either excessive reabsorption from* the bowel or impaired renal conservation of base, with obligatory chloride ion retention, most likely a combination of the two Thus it would seem that while moderate electrolyte imbalance occurs in a majority of these patients, severe changes probably do not occur in the absence of renal damage

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[9] Nesbit, R M J Urol , **61** 728–734, 1949
[10] Cordonnier, J J J Urol , **63:** 276–285, 1950
[11] Boyd, J D Am J Dis Child **42·** 366–371, 1931
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[13] Ferris, D D and Odel, H M J A M A , **142:** 634–641, 1950
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The findings of hypokalemia in nine of eleven cases here studied confirms the findings of others.[17, 18, 19] D'Agostino's studies may readily account for this loss. Blood levels of sodium are less regularly affected. Berliner[20] points out that with renal tubular damage there may be an impairment of the carbonic anhydrase mechanism, allowing potassium and sodium to compete with the hydrogen ion in tubular interchange, contributing further to acidosis and hypokalemia.

SUMMARY

Twelve patients, nine males and three females, with exstrophy of the bladder who underwent ureterosigmoidostomy are herein studied.

Pyelography, growth and development, radio-opaque enema studies, and electrolyte profiles were carried out.

Seventeen of twenty-three pelves studied by excretory urography 4 weeks to 11 years after surgical diversion of the urinary stream were found to be normal or unchanged whereas only twelve of 23 ureters were free of dilatation.

One ureteropelvic system disclosed recto-ureteral reflux, as determined by skiodan enema, and repeated aeropyelograms.

Weight gain in children undergoing ureterosigmoidostomy in general does not proceed in a normal fashion.

All patients disclosed at some time some degree of hyperchloremia.

Eight of eleven patients showed reduction of their alkali reserve on at least one examination.

Nine of eleven suffered some reduction in blood potassium.

The authors wish to acknowledge with appreciation the invaluable aid rendered by Dr. Malcolm Holliday, Department of Pediatrics, in the electrolyte balance studies.

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CARCINOMA COMPLICATING VESICAL DIVERTICULUM

RAYMOND F MAYER AND THOMAS D MOORE

Many case reports of carcinoma arising in vesical diverticula have appeared in the literature within the past 25 years This condition was once looked upon as a clinical rarity, but as the means of diagnosis has improved, it is being recognized more often, and to date approximately 150 cases have been reported We are reporting 8 additional cases primarily to emphasize the importance of the closest scrutiny of all vesical diverticula so that this serious and often obscure complication may not be overlooked

SEX AND AGE

Since diverticulum of the bladder is predominately a disease of the male, it follows that the majority of the cases of carcinoma arising within diverticula occur in men Smith and Suder gave the ratio as 30 men to 1 woman, only 3 cases having been reported in women to date The age varied from 39 to 86 years, the largest number occurring in the fifth and sixth decades In the series we are reporting, there were 7 men and 1 woman, the ages varying from 53 to 72 years

SYMPTOMATOLOGY

There have been no specific symptoms attributed to this condition other than hematuria, gross or microscopic, which was present in 80 to 90 per cent of the reported cases It occurred in 7 of the 8 cases in this series The duration of the hematuria, which was intermittent and of the total and terminal types, varied from 2 weeks to 10 months

DIAGNOSIS

The diagnosis of this condition may be difficult as manifested by the large percentage of cases which were not recognized prior to surgery or necropsy, comprising approximately two thirds of the reported cases, as noted by Petkovic Deming stated in 1927 that it was impossible to make a positive diagnosis of vesical diverticulum without cystoscopy and warned that the cystoscope may not disclose an indwelling tumor unless it protruded through the ostium He was of the opinion that cystography was an aid in demonstrating a diverticulum but that it was probably of little value in establishing the presence of a tumor within it Commenting further upon the value of cystography in diagnosing this condition, Kretschmer and Barber in 1929 warned that the absence of a filling defect in a diverticulum did not exclude a tumor Conversely, we would like to emphasize that demonstration of a filling defect by a cystogram is not necessarily diagnostic of tumor, as other conditions, such as ray permeable calculus, blood clot and gas may produce similar changes The cystogram, therefore, furnishes information that may indicate a tumor, but the findings always should be checked by cystoscopy

Read at annual meeting, American Urological Association Atlantic City, N J June 23 26, 1952

Hunt observed in 1929 that the diagnosis of vesical diverticulum was being made very accurately, but that the preoperative recognition of tumor within the diverticulum was somewhat difficult and usually was not accomplished unless neoplastic tissue projected into the bladder. Higgins in 1936 emphasized the same observations and also pointed out the significance of blood escaping from the ostium of a diverticulum.

A review of 93 cases by Abeshouse and Goldstein revealed that correct preoperative or ante mortem diagnosis was made in only 33 cases. In 18 cases cystoscopy revealed the presence of a diverticulum, but the indwelling tumor was not recognized until the time of diverticulectomy.

A recent review of 25 cases by Boylan, Greene and McDonald revealed a correct preoperative diagnosis in 20 cases, 19 having been made by cystoscopy and 1 by cystography. In the series discussed here, correct preoperative diagnosis was established in 6 cases; although in one instance (case 3) repeated cystoscopies were necessary. Two cases were not definitely recognized until the time of diverticulectomy; one (case 4) was totally unexpected, and the other (case 2) had been suspected because of a filling defect in the cystogram (fig. 1, *A*) but repeated cystoscopies had failed to confirm the diagnosis.

Whenever possible the examining instrument should be inserted into the diverticulum and its interior closely inspected. In spite of observing this rule, a certain percentage of tumors probably will be missed because of their small size and location within the diverticulum. This procedure is applicable primarily to larger diverticula; but a tumor may arise in a diverticulum of any size, as occurred in one of our cases where the capacity was less than 30 cc.

PATHOLOGY

The majority of tumors within vesical diverticula are of epithelial origin. Of the cases being reported, three were grade I, two grade II, two grade III transitional cell carcinomas, and one was an undifferentiated carcinoma grade IV. In

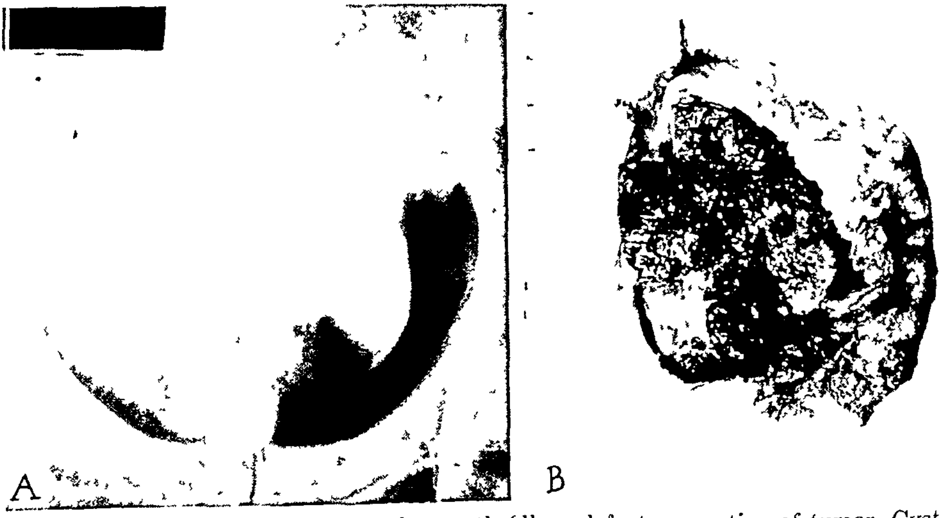

FIG. 1. Case 2 *A*, vesical diverticulum with filling defect suggestive of tumor Cystoscopy was negative *B*, tumor of vesical diverticulum found at diverticulectomy.

5 cases there was either gross or microscopic evidence of invasion of the wall of the diverticulum at the time of surgery. The 3 deaths occurred in this group. There have been no deaths or recurrences in the noninvasive cases.

PROGNOSIS

Since Kretschmer's report in 1940 concerning the regression of vesical diverticula, with disappearance of subjective symptoms, following the correction of vesical neck obstruction, there has been a steady decline in the number subjected to diverticulectomy. As a result of this trend, an obscure tumor within a diverticulum may be undisturbed at a time when it might be easily controlled by diverticulectomy, only to become inoperable at some later time should it not be recognized. Spence and Baird have recently referred to diverticulectomy as a neglected operation which should be performed as a primary procedure whenever retention is demonstrated, irrespective of the size of the sac, along with or followed by correction of the vesical neck obstruction. By adhering to the latter concept, it is possible that a greater number of carcinomas complicating vesical diverticula might be removed at a stage which would result in a more favorable prognosis.

Four of this series are alive and free of residual cancer 7 to 36 months following diverticulectomy. One patient who was treated conservatively because of his cardiac condition and obvious extension of the highly malignant tumor (grade IV) beyond the diverticulum, has survived 6½ years and, astonishingly, is free of urinary symptoms. Two patients died at intervals of 5 weeks and 9 months following diverticulectomy of causes directly related to the malignancy. One patient (case 3) died of generalized carcinomatosis 3 months following exploratory laparotomy, when it was discovered that the neoplasm had extended beyond the diverticulum. Careful examination, including cystography and cystoscopy, of this patient 3 months previously had revealed the presence of vesical diverticula, but a complicating tumor was not demonstrated.

TREATMENT

The treatment of carcinoma complicating a vesical diverticulum may be classified as conservative or radical, depending upon the general condition of the patient, the size and location of the tumor, the degree of malignancy, and the presence or absence of extension beyond the diverticulum. By conservative management is meant transurethral resection of the accessible portion of the tumor, followed by electrocoagulation and implantation of radium or it may consist only of radiation. Radical treatment is characterized by complete removal of the diverticulum and the tumor along with a margin of bladder adjacent to the ostium or even total cystectomy. This can be accomplished transvesically or extravesically, the former preferably because it permits careful examination of the bladder and diverticulum prior to proceeding with the diverticulectomy. In view of the poor results, with the majority of patients surviving less than 2 years, and the high incidence of recurrence, it becomes apparent that much is to be desired in the management of carcinoma involving a vesical diverticulum. Earlier diagnosis would certainly improve the prognosis, and the consideration of more radical types of surgery, such as total cystectomy with regional gland dissection and transplantation of the ureters would likely increase the salvage rate.

CASE REPORTS

Case 1. C. R. E., a 67 year old white man, was admitted to the hospital on December 12, 1945, because of intermittent, painless hematuria of 6 months' duration. Bimanual palpation revealed an indurated irregular mass in the right pelvis which was fixed. Cystography demonstrated a diverticulum of about 100 cc capacity arising from the right wall of the bladder in which was an irregular filling defect. This was interpreted as a carcinoma arising within the diverticulum. Cystoscopy confirmed the presence of a diverticulum in the right wall of the bladder, and neoplasm was seen projecting from the ostium. A biopsy was obtained and reported as grade IV undifferentiated carcinoma. Because of severe coronary disease and the poor general condition of the patient, it was decided to employ conservative measures. The accessible portion of the tumor was resected transurethrally under spinal anesthesia on December 17, 1945. The remaining portion of the tumor was thoroughly electrocoagulated and six platinum needles, each containing 5 mg. of radium were implanted after the method of Moore. The radium was removed cystoscopically under pentothal sodium anesthesia 72 hours later, for a total of 2160 mg. hours. He was dismissed from the hospital 13 days later with instructions to return after 3 months for inspection of the bladder. He has failed to return but recent reports reveal that he is still living after 6½ years, and, surprisingly, has had no further bladder symptoms.

Case 2. L. L. D., a 72 year old white man, was admitted June 27, 1949, because of urinary difficulty and frequency of approximately 6 years' duration, during which time he had undergone three transurethral prostatic resections. The last two resections had been performed within the past 6 months during which time total and terminal hematuria had been noted at irregular intervals. On both occasions a diverticulum of 200 cc capacity was noted arising from the left base of the bladder; endoscopic inspection of its interior had failed to reveal a tumor. Cystography revealed the bladder to be irregular in contour with a moderate-sized diverticulum on the left side, the lower margin of which was irregular in outline, suggestive of a tumor within the diverticulum, but cystoscopy with inspection of the interior of the sac failed to confirm the suspicion (fig. 1, *A*). Because of persistent infected residual urine, a diverticulectomy was performed on June 30, 1949. The diverticulum was approached extravesically, and during its mobilization, an indurated mass was palpated in the region of the base of the sac. The bladder was then opened and a finger introduced through the ostium of the diverticulum, identifying a firm pedunculated tumor measuring 3 cm. in diameter which was located behind the lower margin of the ostium. The excised diverticulum measured 7.2 cm. in its greatest diameter, and the tumor was 3.5 cm. in diameter (fig. 1, *B*). The microscopic diagnosis was transitional cell carcinoma, grade II, arising within the diverticulum and invading its wall (fig. 2, *A*). He returned six months later and cystoscopy revealed extensive recurrence with involvement of practically the entire bladder. He refused further examination or

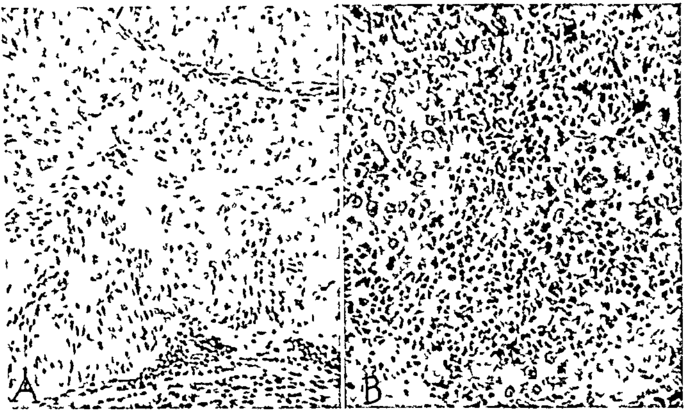

FIG 2 A, case 2 Photomicrograph Grade II transitional cell carcinoma arising in vesical diverticulum B, case 8 Photomicrograph Grade III transitional cell carcinoma in vesical diverticulum

treatment and when last seen 3 months later there was severe dysuria and an indurated mass in the suprapubic region The referring physician reported that the patient expired about 3 months later of generalized carcinomatosis

Case 3 H B J , a 68 year old white man, was admitted September 20, 1949, because of intermittent hematuria, initial and terminal, of 10 months' duration, associated with frequency and dysuria Approximately 4 months previously he had undergone a transurethral prostatic resection because of urinary difficulty and frequency, when a large diverticulum was reported on each side of the bladder, neither of which revealed evidence of a tumor by cystography or cystoscopy He remained well approximately 3 months when gross hematuria recurred At cystoscopy a necrotic tumor was noted in the dome of the diverticulum on the left side of the bladder A biopsy was reported transitional cell carcinoma grade II Bimanual palpation revealed an indurated mass in the left pelvis which was thought to be movable, therefore, diverticulectomy was advised Exploration revealed extensive local and distant metastases rendering the condition inoperable He was dismissed from the hospital on the seventh day and expired 2 months later of generalized carcinomatosis

Case 4 C B C , a 68 year old white man, was examined September 19, 1949, because of urinary difficulty and frequency of 3 years' duration Gross hematuria had not been noticed Cystography revealed a moderate degree of intravesical prostatic enlargement, with numerous small prostatic calculi, an irregular bladder outline and a diverticulum of about 200 cc capacity on the left side It was decided to correct the prostatic obstruction and observe the amount of retention remaining in the diverticulum A transurethral prostatic resection was performed on September 23, 1949, at which time careful inspection of the bladder and the interior of the diverticulum failed to reveal evidence of tumor He continued to carry from 180 to 240 cc of residual urine; therefore, removal of the diverticulum was advised. A combined transvesical and extravesical diverticulectomy was performed under spinal anesthesia on October 18, 1949. Inspection of the interior of the excised sac revealed a small papillary tumor in the base near the ostium; this was an unexpected finding. The microscopic diagnosis was transitional cell carcinoma grade I arising within a diverticulum and showing no evidence of invasion of the wall. He is now asymptomatic, and there has been no evidence of recurrence of the tumor 36 months after diverticulectomy.

Case 5. G. C., a 67 year old white man, was examined May 25, 1951, because of intermittent gross hematuria of approximately 6 months' duration. Examination revealed a moderate degree of prostatism along with a diverticulum in the right base of the bladder. A pedunculated tumor was noted within the diverticulum attached by a narrow stalk near the inferolateral margin of the ostium. Because of cardiac disease, it was decided to transurethrally resect the obstructing prostate and the tumor within the diverticulum. The pathologist reported benign hyperplasia of the prostate and transitional cell carcinoma grade II of vesical diverticulum. He returned after 3 months for further observation still complaining of gross hematuria. Bimanual palpation revealed an indurated mass in the right pelvis, which was thought to be movable. Endoscopic examination revealed the diverticulum to be filled with neoplasm. Since the tumor had recurred 3 months following its transurethral resection, a combined transvesical and extravesical diverticulectomy was performed May 29, 1951. The diverticulum was distended with tumor which protruded through the ostium. There was evidence of extension of the tumor through the wall of the diverticulum in the region of the iliac vessels making sharp dissection necessary. Roentgen therapy was started on the eighteenth postoperative day, and his course was uneventful until the twenty-eighth postoperative day when respiratory difficulty suddenly developed, rigors and fever and evidence of circulatory collapse. His condition gradually deteriorated terminating in death on the thirty-sixth day after operation. The clinical impression concerning the immediate cause of death was pulmonary embolism; necropsy was not permitted.

Case 6. F. B. M., a 68 year old white man, was examined July 12, 1951, because of intermittent gross hematuria of 10 months' duration. A pneumocystogram demonstrated grade I intravesical prostatic enlargement with suggestion of a small diverticulum on the left side of the bladder. This was confirmed by a fluid cystogram which also disclosed two small filling defects within the diverticulum. Cystoscopy revealed a mild degree of prostatic obstruction, chiefly of the bar type, along with a small diverticulum arising from the lower right wall of the bladder. While the diverticulum was being observed, a small papillary tumor could be seen moving in and out of the ostium as the patient breathed. Due to the presence of the neoplasm within the small diverticulum a transvesical diverticulectomy and suprapubic resection of the prostatic bar were performed on July 16, 1951. The tumor proved to be grade I transitional cell carcinoma arising within the diverticulum. Cystoscopy at 3 month intervals has been negative; the last visit was nine months following the operation.

Case 7. J. W. D., a 65 year old white man, whose presenting symptoms were dysuria and terminal hematuria of two weeks' duration. Air cystography disclosed a filling defect in the right base of the bladder adjacent to a small diverticulum. Cystoscopy confirmed the presence of a neoplasm in the right base of the bladder. It measured approximately 2 cm. in diameter and apparently was attached by a narrow pedicle inside the ostium of a shallow diverticulum. A suprapubic transvesical diverticulectomy, including the tumor and a 2 cm. margin of bladder surrounding the ostium, was performed on September 14, 1951. The diverticulum measured 3 cm. in diameter, and the attachment of the tumor was definitely identified as arising inside the ostium. The microscopic diagnosis was transitional cell carcinoma, grade II, within a diverticulum, and there was no evidence of invasion of the wall. He was dismissed from the hospital on the seventeenth postoperative day and cystoscopy at 3 month intervals has been negative, the last examination being nine months after diverticulectomy.

Case 8. B. C., a 54 year old white woman, was examined October 13, 1951 because of gross, painless hematuria of 1 month's duration. Cystography demonstrated a diverticulum measuring approximately 5 cm. in diameter on the left side of the bladder. There was a small filling defect along its upper border (fig. 3, *A*). Cystoscopy confirmed the presence of a diverticulum; however, it was necessary to introduce the cystoscope within the diverticulum before the sessile tumor on its upper wall could be visualized. A combined transvesical and extravesical diverticulectomy was performed through a suprapubic incision on October 15, 1951. There was no gross evidence of extension of the neoplasm beyond the diverticulum (fig. 3, *B*). The microscopic diagnosis was transitional cell carcinoma grade III (fig. 2, *B*), arising within a diverticulum and invading its wall. The postoperative course was uneventful; the patient was dismissed from the hospital on the tenth day. She was instructed to have the bladder inspected at 3 month

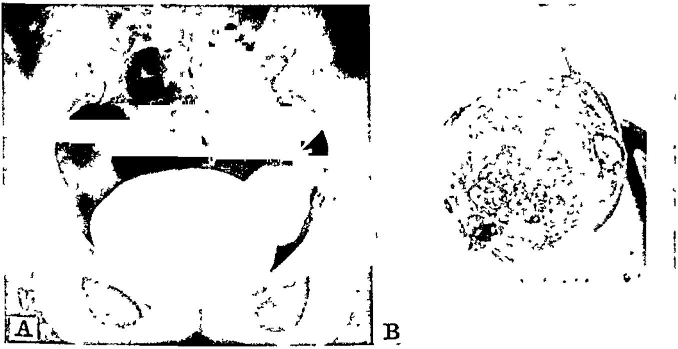

Fig 3 Case 8 *A*, vesical diverticulum. Note filling defect in upper margin. Cystoscopy demonstrated tumor at this site *B*, surgical specimen; vesical diverticulum which has been everted over Foley bag showing small carcinoma.

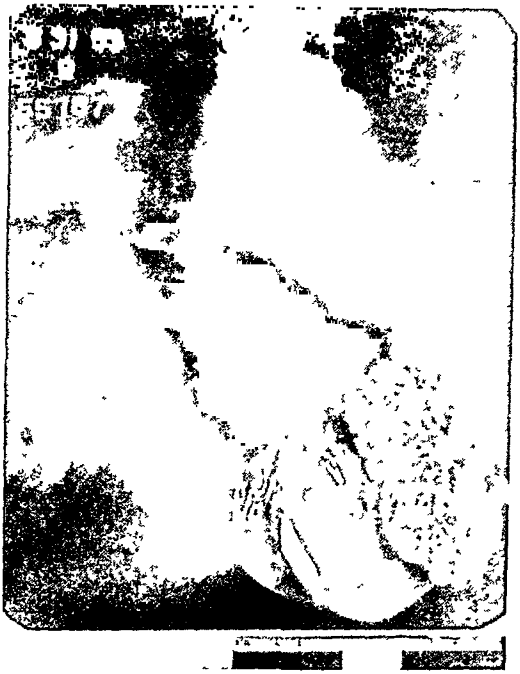

FIG. 4. Pneumocystogram revealing huge infiltrating carcinoma in an unusually large vesical diverticulum together with operative specimen.

intervals and this has been done in another city with negative findings after 6 months.

ADDENDUM

Since the manuscript was submitted for publication, we have had a case that is an outstanding example of a huge carcinoma within a diverticulum (fig. 4).

SUMMARY

Carcinoma complicating vesical diverticulum is a relatively infrequent clinical entity somewhat difficult to diagnose at a time when treatment would be most effective. Hematuria is the most frequent symptom, occurring in 80 to 90 per cent of cases. The diagnosis is easily established when the tumor protrudes through the ostium of the diverticulum into the bladder, but this occurs in only a small percentage of cases, or late in the disease. The importance of careful examination of vesical diverticula, including cystography and the endoscopic inspection of their interior, is stressed in order that the frequency with which this condition is overlooked might be reduced. Eight cases have been critically analyzed; the results suggest the importance of earlier diagnosis and a more radical type of surgical treatment than has been employed in the past. Since a sizable number of cases have not been recognized until the time of diverticulectomy, it would appear this procedure should be employed more frequently. The survival rate is in direct proportion to the degree of infiltration of the wall of the diverticulum by the tumor.

899 Madison Ave., Memphis 8, Tenn.

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CARUNCLE OF THE POSTERIOR URETHRA AND BLADDER NECK

WALTER A. SCHLOSS

The literature on urethral caruncle varies from a master's thesis in Urology[1] to a recent article by Begg[2] stating bluntly that "There are no urethral caruncles."

The word "caruncle" means "a little bit of flesh." It is believed that the English surgeon, Samuel Sharp in 1750 first described urethral caruncles.[3] It has also been called "vascular tumor of the meatus." It is generally understood to be a growth of the lower half of the external urethral orifice in the female. However, caruncles are by no means confined to the posterior half of the external urethral meatus. McKim, Smith and Rush[4] in reviewing 202 cases of urethral caruncle, found only 5 per cent external to the meatus, in women with a wide meatus; 95 per cent were described as "intra-urethral," located just inside the external urethral orifice, behind a tight meatus; 99.7 per cent were on the posterior surface. They also took note of a so-called "urethral flap," a small localized protrusion of tissue on the posterior surface of the urethra. Clinically this bears no resemblance to caruncle, but it may be a precursor. It is usually seen when there is a wide external urethral meatus.

Begg[2] believes that all caruncles are partial prolapses of the urethral mucosa. He states that the condition is caused or at least accompanied by, infection of the kidneys, bladder, urethra or cervix. We do not believe that Begg's tenets are substantiated by the facts, because, as will be shown, caruncles may be found in the absence of infection, they may be found within the urethra up to and including the bladder neck, and their histopathology is rather precise.

A classification of caruncles has been given by Gutierrez,[5] who states that there are three types: 1) those external to the meatus; 2) those internal to the meatus; 3) mixed, those partly in and partly outside the meatus.

The histopathology of urethral caruncle has been divided by Novak[6] into 3 chief types: 1) papillomatous; 2) telangiectatic or angiomatous; 3) granulomatous.

A somewhat different histopathological classification is given by Friedman and Ash, of the Armed Forces Institute of Pathology.[7] They believe that the urethral caruncle has a triphasic life history, to wit:

1) Polypoid stage: This is a small polypoid nodule which results from ectropion

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[1] Palmer, J. K., Emmett, J. L. and McDonald, J. R.: Surg., Gynec. & Obst., **87:** 611, 1948.

[2] Begg, R. C.: The Lancet, **240:** 824, 1951.

[3] Sharp, Samuel: A Critical Enquiry into the Present State of Surgery. London: J. & R. Tonson, 1750, p. 168 (cited by Gutierrez, Robert[5] and by many others).

[4] McKim, G. F., Smith, P. G. and Rush, T. W.: J. Urol., **49:** 187, 1943.

[5] Gutierrez, Robert: Urol. & Cutan. Rev., **40:** 223, 1936.

[6] Novak, E.: Gynecological and Obstetrical Pathology. Philadelphia: W. B. Saunders Co., 1941, p. 29.

[7] Friedman, N. B. and Ash, J. E.: Atlas of Genitourinary Pathology. Washington, D. C.: Army Institute of Pathology, 1946, p. 190, 192.

of the meatus, prolapse of the urethra, or simple edema Histologically, the lesion shows edematous connective tissue covered by stratified squamous epithelium

2) Granuloma stage Histologically there is epithelial proliferation due to secondary inflammation with lymph follicles and hyperplastic, inflamed, periurethral glands

3) Angiectatic or vascular stage This shows pseudo angiomatous angiectasia and thrombosis due to vascular stasis This gives the typical bleeding, painful lesion seen clinically at the external urethral meatus

These authors furthermore state that "The true caruncle is a specific lesion Its histologic appearance varies with the stage of its evolution "

In the differential diagnosis of caruncle may be mentioned the following [8]

1) Polyps Usually multiple, may be cystic

2) Papilloma A benign pluriglandular growth which may arise from any portion of the urethra

3) Urethral prolapse (Cf Begg) Involves entire circumference of the external urethral meatus

4) Varicosities Bluish, elastic, readily reduced by compression

5) Peri urethral abscess and abscess of Skene's glands Inflammatory lesions, with leukocytic infiltration and pus

6) Condyloma of the urethra Multiple, warty, fungus like growths

7) Urethral diverticula and urethroceles Distinguished by urethroscopy and urethrography

8) Ureterocele presenting at external urethral meatus Distinguished by urography and cystoscopy

9) Urethral carcinoma Last but not least, every lesion should have a biopsy In 100 cases of caruncle, of which 47 were studied pathologically, Walther[9] found 5 cases of unsuspected carcinoma of the urethra and 2 "precancerous lesions " In this regard, it is noted in *Progress in Gynecology*[10] that "The urethral caruncle, although statistical proof is not available, has a recognized association with malignant disease In lesions at the external meatus, the differential diagnosis will include papilloma, prolapse of the urethral mucosa, and caruncle, as well as carcinoma Biopsy should always be taken "

As to the symptoms of urethral caruncle, they are well known to all—from no symptoms whatever to excruciating pain and tenderness, with frequency, dysuria, hematuria and dyspareunia They are also given as a cause of post menopausal bleeding in some cases [11]

In describing an operation for the treatment of resistant urethral caruncle, Deming[12] mentions the fact that "some caruncles respond to most any procedure " At any rate, treatment, always including biopsy, of urethral caruncles at the external urethral meatus, may be by any of the following 1) excision with fulguration of the base;[13] 2) excision by high frequency current;[9, 14] 3) excision by the operation of Deming,[12] or Moore.[15] (For cases with rigid bladder necks and exuberant tissue at the external meatus or along the urethral canal or at the bladder neck—caruncles, polypoid excrescences, etc.—that do not yield to office treatment, Moore recommends dilatation of the urethra to ¾ inch in diameter with the Goodell cervical dilator, under spinal or sacral anesthesia. Then, with the urethra wide open through its entire length, all caruncles and exuberant tissue are cut away by sharp scissors. After this, coagulation of the bleeding surfaces is performed. A Foley catheter is left indwelling for 5 or 6 days. As far as I know, this procedure has not gained wide popularity.)

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[8] Palmer J K et al loc cit [1]

[9] Walther H W E J Urol 50 380, 1943

[10] Meigs J V and Sturgis S H Progress in Gynecology, (Ch IX, Langdon Parsons, and Ch X Roger C Graves) New York Grune and Stratton 1946

[11] Wharton L R Gynecology and Female Urology Philadelphia W B Saunders Co, 1943 p 938

[12] Deming C L New Eng J Med, 205 484, 1931

THE PROBLEM OF THE POSTERIOR URETHRA

Having reviewed urethral caruncles as they are ordinarily considered, let us turn our attention to the problem at hand, caruncles of the posterior urethra and bladder neck.

In 1931, Folsom[16] reviewed the embryology, anatomy, histology and pathology of this region, and ventured the opinion that the posterior urethra had been a much neglected field of study. He made the point that the posterior urethra was often the site of pathological changes which were the cause of many subjective symptoms, in patients in whom the remainder of the urinary tract was found to be normal. Furthermore, lesions of the posterior urethra were often found in patients who had had varied and severe symptoms ascribed to the pelvic generative organs, and in whom surgery directed toward the uterus, tubes, ovaries, cystocele, etc., had failed to bring relief of their symptoms.

In a further discourse on this subject, Folsom[17] speculates as to the pathogenesis of these lesions of the posterior urethra. Glands of a rudimentary type are found in the posterior urethra in the female. These, as rudimentary structures, are more susceptible to disease (viz. the appendix) than highly organized and better developed organs. Experimental work by Korenchevsky, cited by Deter, Caldwell and Folsom,[18] in which injection of male hormones in female rats caused the urethral glands to hypertrophy, gave rise to speculation by Deter et al. that the deficiency of female sex hormones when the female enters the menopause may cause hypertrophy of the glands of the female posterior urethra and thus make them more susceptible to infection. Now, should the glands found in the female posterior urethra become infected, and should these nests become surrounded by fibrous or thickened epithelial tissue, cure would be difficult without some form of surgery. I quote from this interesting paper: "Posterior urethral disturbances and urethral obstruction in females are not new entities in themselves; the accurate interpretation of the clinical findings is of a more recent date."

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[13] Everett, H. S.: Gynecological and Obstetrical Urology. Baltimore: Williams & Wilkins. 1944.

[14] Lowsley, O. S. and Kirwin, T. J.: Clinical Urology. Baltimore: Williams & Wilkins, 1944, ed. 2.

[15] Moore, N. S.: South. Med. J., **38:** 149, 1945.

[16] Folsom, A. I.: J.A.M.A., **97:** 1345, 1931.

[17] Folsom, A. I.: South Med. J., **25:** 859, 1932.

[18] Deter, R. L., Caldwell, C. J. and Folsom, A. I.: J. Urol., **55:** 650, 1946.

I should like now to report what is not truly a new entity, but rather a new concept of what must be an old condition, previously but little recognized It is new in that such lesions of the posterior urethra have been described grossly[16–19] but *never named* as specific pathologic entities—namely, caruncles of the posterior urethra and bladder neck, and it is new in that the treatment prescribed is different from what has been usually described for afflictions of the posterior urethra except for obstructive lesions at the bladder neck in females The lesions to be described herein are *not* obstructive

CASE REPORTS

Case 1. Hartford Hospital No 695336, a 53 year old white married woman was seen on May 22, 1951 complaining of burning on urination, dysuria, frequency and nocturia, and occasional dull pain in the right lower quadrant, of 2 months' duration, and dyspareunia of 3 months' duration She had been treated by her gynecologist with Gantrisin because of suspected cystitis and mild pyuria The pyuria had cleared but the symptoms had not, and she was referred for urological opinion Catheterized urine analysis was entirely negative, including the microscopic examination The urine culture was no growth The residual urine was 10 cc There were no findings on examination of the back or abdomen The external genitalia were normal Cysto-urethroscopy with the foroblique panendoscope revealed polypoid nodular excrescences at the bladder neck at 6 and 8 o'clock (fig 1) When the end of the instrument impinged upon these excrescences, the patient suffered severe pain similar to her present complaint

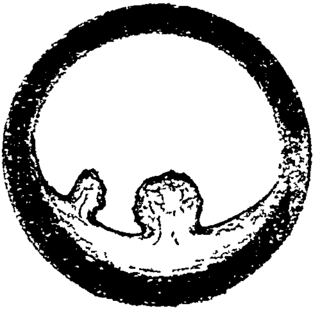

Fig 1 Case 1 Nodules at bladder neck as seen with foroblique panendoscope

The patient was admitted to the Hartford Hospital on June 1, 1951 and cystoscopy repeated the following day under thiopental sodium anesthesia Bilateral retrograde pyelography was negative Culture of urine from each kidney and from the bladder revealed no growth The bladder was normal, distending uniformly and well The urethral polypoid excrescences at the bladder neck were then resected with the Stern-McCarthy resectoscope A 16F Foley catheter with

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[19] McCrea, L E Clinical Cystoscopy Philadelphia F A Davis Co , 1946, p 920

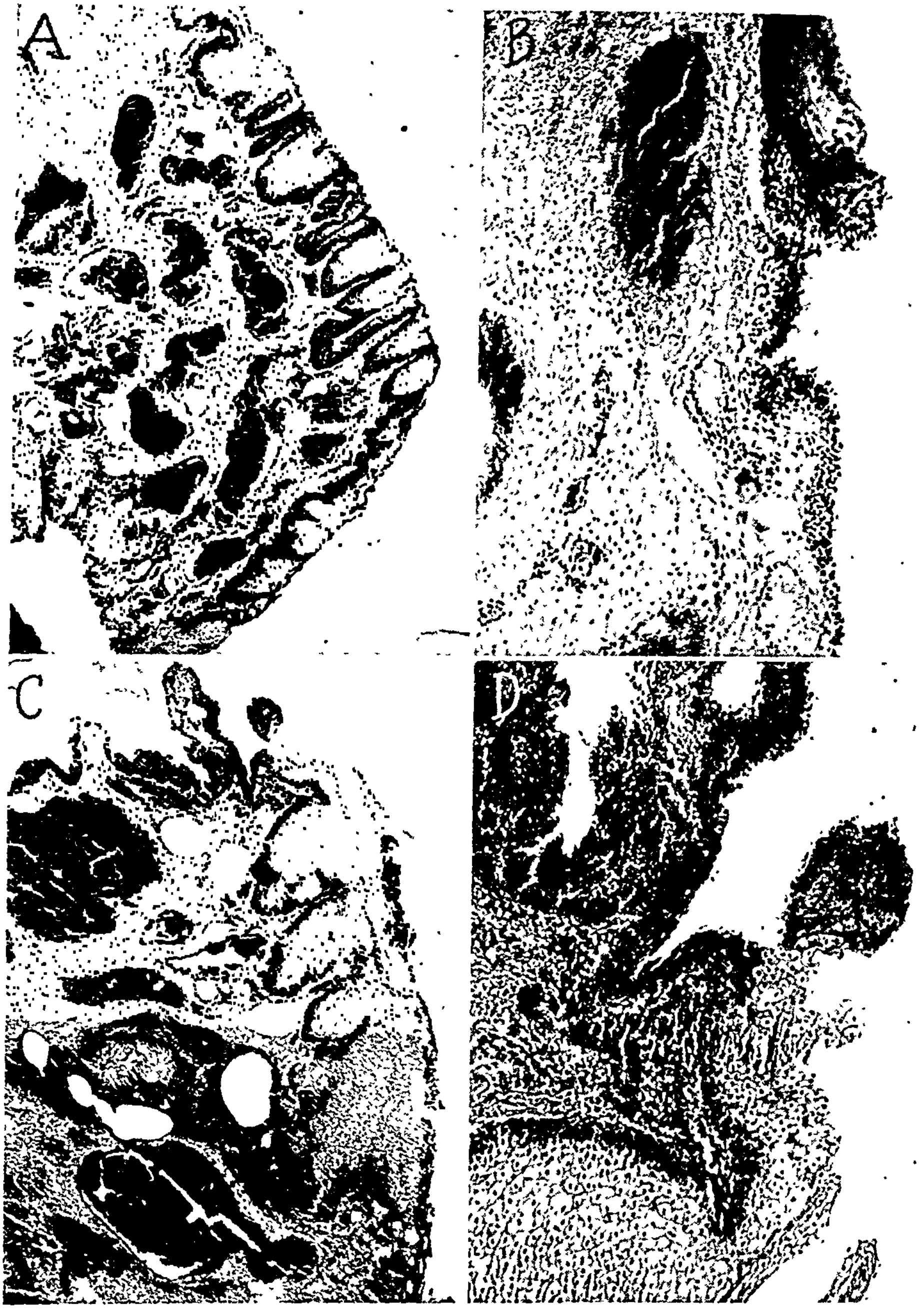

FIG. 2

5 cc bag was left indwelling for 24 hours. When it was removed, Pyridium was given in anticipation of burning on urination, which was, however, very mild.

The specimen (fig. 2, *A*) showed dilated blood vessels with columnar glands with thickened epithelium, typical of urethral caruncle (Robert Tennant, M.D., pathologist).

After discharge, the patient had some urgency and burning intermittently for a period of 3 weeks. By July 6, 1951, one month postoperatively, she still had a little frequency and dysuria, but no nocturia, and no incontinence. She felt well and was able to sleep all night. Coitus had not yet been attempted.

Six months follow up revealed that the patient had occasional transient episodes of burning on urination, but "nothing like it had been before the operation." Intercourse was now possible, although infrequent. She was able to sleep 8 hours without having to get up to void and voided about every 4 hours during the day.

Comment: The patient had been told at one time that her urinary symptoms were due to a cystocele. The gynecological consultant, however, did not believe that the moderate cystocele (without stress incontinence) was the cause of her symptoms, and that operation for the cystocele was contra-indicated, referring her for urological consultation instead.

Case 2. Mt. Sinai Hospital No. 50 618, a 63 year old white married woman was first seen June 2, 1951 complaining of frequent scalding urination and urgency incontinence of 4 or 5 years' duration. One year previously cystoscopy had been done elsewhere, at which time urinalysis was negative, cultures from both kidneys and bladder showed no growth, and retrograde pyelograms were normal.

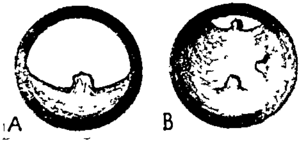

FIG. 3. Case 2. *A*, nodule at bladder neck. *B*, nodular excrescences in posterior urethra

Fulguration of papillary excrescences at the bladder neck had been done, but they had not been resected or biopsied, and no tissue had been sent to the laboratory. This procedure had given only partial and temporary relief.

The patient was admitted to Mt. Sinai Hospital, Hartford on June 4, 1951. On June 6, 1951, under spinal anesthesia, cysto-urethroscopy was carried out. The upper urinary tracts were normal by retrograde pyelography. Culture of urine from both kidneys and the bladder showed no growth. The bladder appeared normal, but at the bladder neck just within the posterior urethra, there was a nodular excrescence at 6 o'clock (fig. 3) and there were two others in the posterior urethra about 0.5 cm. from the bladder neck, at 3 and 6 o'clock. These "growths" were resected with the Stern-McCarthy resectoscope and their bases fulgurated. At the conclusion of this procedure, the urethra and bladder neck were quite clean and smooth and there was no bleeding. A 16F Foley catheter with 5 cc bag was left indwelling.

The gross specimen consisted of three small pieces of tissue the largest of which measured approximately 8 mm. in diameter. One of them was flat and discolored brownish as if burned. The other two were ovoid and had upon their surfaces smooth surfaced, rounded elevations measuring approximately 5 mm. in greatest diameter. The pattern was suggestive of a caruncle. Microscopically (fig. 2, *B*), the specimen consisted of several small pieces of tissue showing recent dense fibrous tissue overlying the supporting structures. The surface shows residue of moderately disturbed epithelial covering and nodules of large size composed entirely of heaped up fibrosed granulation tissue. Diagnosis: Caruncle (E. R. Studenski, M. D., pathologist).

The catheter was removed on the first postoperative day and the patient voided with very little burning or dysuria. She was discharged on the second postoperative day on Donnatal 2 tablets 3 times daily because of urgency, with occasional urgency incontinence.

The patient's chief difficulties following the transurethral resection of the caruncles at the bladder neck and posterior urethra were concerned with urgency, and, at times, urgency incontinence while on her feet, as well as constipation, which latter had troubled her all her life. These urinary symptoms gradually subsided over the next two weeks. The urgency disappeared and then one month postoperatively the patient complained of terminal dysuria, and Donnatal was again given; the urinalysis was negative and the urine culture no growth.

Six months follow up report from the patient revealed that she was voiding well, without pain, frequency, urgency or burning. Her only urinary complaint was stress incontinence, on sneezing and coughing, which she had had for years, to a minor degree.

Comment: It is noteworthy that this patient had had papillary excrescences at the bladder neck fulgurated with the Bugbee electrode one year prior to the time I first saw her. It was evident from this that there were nodules in the posterior urethra and bladder neck at an earlier date and that the patient did not obtain relief until these nodules were *resected* and their bases fulgurated. Time will tell whether her trouble will recur.

Case 3. Hartford Hospital No. 701578, a 41 year old white married woman had been treated by various physicians, including myself, numerous times in the past 2 years for "cystitis and trigonitis." Relief with various medications was temporary and insubstantial. On cystoscopy in August 1950, I found that the trigone was peppered with little red petechiae. The urine culture at that time was negative and the urine showed only 3 to 4 white blood cells per high power field, on a centrifuged specimen. Residual urine was 5 cc.

She returned 1 year later with the history of pain in the lower urinary passages before, during and after voiding, radiating into the left groin, of 2 months' duration, with urgency, frequency every hour, and nocturia twice every night. Cystourethroscopy revealed mild trigonitis as far as the bladder was concerned but, in addition, a cystic-appearing papilliferous growth was seen at the bladder neck at 2 o'clock, which was very tender when touched with the end of the instrument (fig. 4).

The patient was admitted to the Hartford Hospital on August 9, 1951. On August 10, 1951, transurethral resection of the papilliferous mass at the bladder neck was accomplished, and the base fulgurated, using the Stern-McCarthy resectoscope. A 20F Foley catheter with 5 cc bag was left indwelling.

The gross specimen consisted of four fragments of tissue each measuring 4 mm in diameter, and having a yellowish-white appearance Microscopic section (fig 2, *C*) shows a fragment of tissue covered by squamous epithelium, with a loose stroma and containing numerous dilated vascular spaces The appearance is compatible with angiomatous caruncle Diagnosis Urethral caruncle (Robert Tennant, M D)

The Foley catheter was removed on the first postoperative day The patient was discharged on the second postoperative day, on Pyridium and Mandelamine, voiding well, complaining only of slight terminal dysuria

The terminal dysuria persisted for about 3 weeks A checkup examination 1 *month postoperatively revealed that the patient voided every 3½ to 4 hours* during the day and had nocturia 1 time There was occasional urgency and burning Urethroscopy revealed some bullous edema at the site of resection and ful-

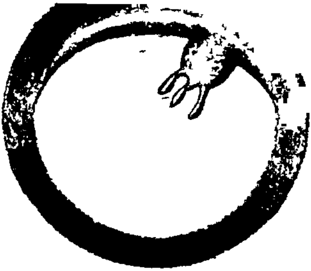

FIG 4 Case 3 "Cystic" papilliferous growth at bladder neck, very tender

guration, but on the whole the bladder neck and posterior urethra had a healthy appearance She was given elixir phenobarbital with tincture belladonna A letter from the patient one month thereafter stated that "The bladder irritation must be all gone because it does not bother me "

Comment This patient had been treated on numerous occasions for symptoms suggestive of cystitis When we saw her, the urine was negative and the culture negative, and the true condition was found by cysto urethroscopy Resection and *fulguration of the caruncles at the bladder neck gave her true relief of her* symptoms for the first time We hope that the relief is permanent, but of course only time will tell This is her longest asymptomatic period in the past 2 years

Case 4 Hartford Hospital No 701682, a 35 year old white married woman was first seen August 6, 1951 complaining of recurrent attacks of frequency, burning, urgency, and nocturia 4 to 5 times per night Burning on urination had first been noticed at the age of 16, and since that time had been recurring at irregular intervals, and gradually increasing in severity In 1932 cystoscopy elsewhere revealed cystitis, urethritis and cystocele The patient was treated with argyrol instillations which gave temporary relief each time At various times she had received Gantrisin, Pyridium, Aureomycin, and Urised, with no relief

The present symptoms were much worse than any previously, and were accompanied by dyspareunia, a new symptom for her. Examination revealed no costovertebral tenderness and the abdomen was soft and without masses or tenderness. A mild cystocele was present, but the genitalia were otherwise normal. Urinalysis showed only an occasional pus cell. The residual urine was less than 10 cc and the urine culture was no growth.

Cysto-urethroscopy showed mild hyperemia of the blood vessels over the trigone, plus granulations of a papillomatous nature in the posterior urethra just distal to the bladder neck at 11 and 1 o'clock (fig. 5). These were decidedly tender on being touched with the panendoscope.

The patient was admitted to the Hartford Hospital on August 10, 1951. The following day, cysto-urethroscopy with pyelography showed normal upper urinary tracts with mild descent of the right kidney in the erect position (1½ lumbar vertebrae) without evidence of hydronephrosis, or trapping, or kinking of the ureter. The papillary granulations in the posterior urethra were then resected with the Stern-McCarthy resectoscope and their bases fulgurated. A 16F Foley catheter with 5 cc bag was left indwelling.

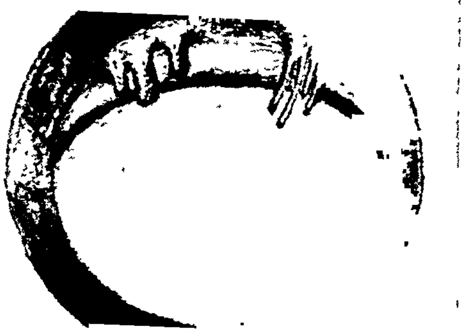

FIG. 5. Case 4. Papillary and villous granulations distal to bladder neck

The gross specimen consisted of 5 small pieces of somewhat hemorrhagic biopsy tissue, the largest measuring 0.5 cm. Microscopically (fig. 2, *D*), the sections showed fragments of fibrous tissue containing numerous dilated vessels filled with blood and lined with squamous and transitional epithelium. Diagnosis: Urethral caruncle.

The catheter was removed on the first postoperative day and the patient placed on Gantrisin and Pyridium. She was discharged on the second postoperative day on the above medication, having some terminal dysuria.

One week after the resection of the caruncles at the bladder neck, the only complaint was morning dysuria (on arising). The remainder of the day she was asymptomatic. There was occasional nocturia, 1 or 2 times.

Six weeks postoperatively, there was only a slight sensation of discomfort at the end of urination There was occasional sneeze incontinence The urine showed only an occasional epithelial cell Cysto urethroscopy with the 20F McCarthy panendoscope revealed an entirely normal bladder, the bladder neck and urethra were clean and smooth The patient was discharged for a 1 year follow up, unless symptoms recurred before that The dyspareunia had completely disappeared

Comment This patient had had frequent recurring symptoms of lower urinary tract "irritation" for 19 years Treatment with various medications and argyrol locally had given evanescent relief, whereas resection fulguration of the caruncles in the posterior urethra near the bladder neck had left her more comfortable than she had been in years

DISCUSSION

It is evident from the paucity of findings on urinalysis and urine culture that the cause of the symptoms in these 4 cases is not now cystitis, although all the patients had been treated for cystitis in the past (when their symptoms could very well have been due to cystitis) Therefore, this gives us a clue as to which patients might be suspected of having caruncles at the bladder neck and/or in the posterior urethra This pathologic entity should be looked for cystoscopically (which should always include urethroscopy with the foroblique lens system) The diagnosis may be suspected in those women who come under the following criteria

1) History of long standing or intermittent lower urinary tract symptoms
2) Essentially negative urinalysis (catheterized)
3) Negative urine culture
4) Treatment with the usual medication and instillations, etc affords transient or no relief
5) Finding the nodules (caruncles) at the bladder neck and/or in the posterior urethra

The diagnosis may be proven by the transurethral resection of these nodules and histologic study of the sections

The treatment is accomplished with the resectoscope, resecting the nodules and then fulgurating the bases We have used a "lighter" current than for trans urethral resection of the prostate, 50 cutting and 30 coagulating, in view of the thinness of the tissues in the female Needless to say, one must not cut too deeply, for fear of perforation or sphincteric injury Two or three excursions of the resectoscope loop will usually suffice to cut away these nodules to their bases

Postoperatively the usual urinary sedatives and antiseptics, and occasionally antispasmodics, may be given

COMMENT

As previously mentioned, there is nothing new about finding nodular excrescences at the bladder neck in the female They are depicted beautifully in Folsom's article in 1931[16] and in McCrea's *Clinical Cystoscopy* in 1946 [19]

However, that some of these excrescences might be urethral caruncles came as rather a surprise to us When the first one was reported, I thought that perhaps there was some mistake. However, on reviewing the slides, it was unmistakably a caruncle. When cases 2, 3 and 4 came along, the same thing happened: in each case the tissue was sent to the pathologist as "resection pieces from the bladder neck," and each was reported to be caruncle. Therefore, we now believe that this (caruncles of the bladder neck and posterior urethra) is a definite entity and should be looked for in all cases wherein there have been symptoms of lower urinary tract irritation without clinical findings to explain them.

We have attempted to be clearcut in our definitions, indications, and therapy. Ewert and Summons[20] have recently described edematous folds, tiny cysts, little villi and polypoid excrescences at the bladder neck in cases of chronic urethritis in the female. Perhaps some of these were caruncles at the bladder neck, but they were not biopsied.

Brown,[21] in describing polypoid formations at the internal orifice, along with vascular papillary projections, may have been seeing some of these "internal caruncles"; however, since he advocated simple fulguration by electrocautery (for chronic urethritis which does not respond to urethral dilatation, nor to bladder irrigation with occasional bladder distention, and instillation of increasing strengths of silver nitrate solution), he would not have had any tissue from the bladder neck to examine histologically.

Cook and Hodgson[22] also noted that, in many cases of granular and cicatricial urethritis, there were localized regions of mucosal proliferation, particularly at the vesical neck, which they referred to as "inflammatory tags." It is possible that some of these "swollen, reddened regions" may have been caruncles of the posterior urethra and bladder neck.

SUMMARY AND CONCLUSIONS

The literature on urethral caruncle has been briefly reviewed, as well as the pathogenesis, pathology, classification and treatment of the urethral caruncles commonly seen at the external urinary meatus in the female.

Four cases of caruncles in the posterior urethra and bladder neck have been presented. This lesion, while undoubtedly nothing new, has not been described as an entity which seems to be not uncommon.

Caruncles of the posterior urethra and bladder neck are best treated by transurethral resection, with fulguration of the base, in our opinion. Tissue so removed should always be sent for histologic study.

Follow-up studies up to 6 months have demonstrated striking relief of symptoms thus far in all four patients.

It seems reasonable to surmise that many cases of so-called "chronic female urethritis" and "irritable bladder" are in reality cases of caruncles at the bladder neck or in the posterior urethra.

99 Pratt St., Hartford 3, Conn.

[20] Ewert, E. E. and Summons, H. J.: Surg. Clin. North Amer., **31:** 671, 1951.
[21] Brown, H. E.: Penna. Med. J., **53:** 489, 1950.
[22] Cook, E. N. and Hodgson, J. E.: M. Clin. North Amer., **29:** 1005, 1945.

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PRIMARY CARCINOMA OF THE MALE URETHRA*

WILLIAM J BAKER, EDWIN C GRAF AND JOHN VANDENBERG

From the Cook County and St Luke's Hospitals, Chicago, Ill

The late diagnosis of primary carcinoma of the anterior male urethra in 13 instances has led us to study the records of these patients Ten of these patients have been seen during the past 5 years

The first report of carcinoma of the male urethra was presented by Hutchinson in 1862 Since that time there have been over 200 case reports of this entity placed in the literature Kreutzmann and Collop wrote a very critical and excellent treatise on this subject in 1939 McCrea and Furlong summarized 230 proven cases of primary carcinoma of the urethra The last report was presented by McCrea and Furlong in 1952 So, this lesion can now be classed as a relatively rare or uncommon one

The diagnosis of carcinoma of the anterior male urethra in each of the following patients was established by histological study of tissues which were obtained from surgical and autopsy specimens

CASE REPORTS

Case 1 J V, a 70-year old white man, was admitted to the hospital on March 14, 1945 His history included two bouts of initial hematuria 5 months before *admission to the hospital Three months before admission he had chills and fever* which were associated with a perineal swelling and pain during micturition The perineal swelling drained spontaneously and he noted that urine escaped through the fistula during micturition Physical examination revealed an indurated and swollen perineum with many purulent sinuses Urethral calibration revealed a filiform stricture of the bulbous urethra The prostate gland was flat and felt benign There were no palpable inguinal lymph glands Cystotomy and radical amputation of the penis and scrotum were performed on April 20, 1945 The postoperative course was stormy and the patient died 3 days later in peripheral vascular collapse Pathological examination of the surgical specimen revealed an infiltrating, hornifying squamous cell carcinoma of the anterior urethra with extension into multiple fistulous tracts (fig 1, *A*)

Case 2 G P, a 64 year old Negro, entered the hospital on December 28, 1945 A peri urethral abscess was drained 4 months before admission Urine had drained from the surgical incision ever since the operation was performed He admitted specific urethritis and much treatment for the control of urethral strictures Physical examination revealed a debilitated and critically ill Negro Many rales were noted throughout the chest Many infected urinary fistulas were noted in the perineum and scrotum Biopsy of a scrotal fistula showed squamous cell carcinoma Debility progressed and death occurred on February 4, 1946 Postmortem examination revealed peri urethral abscess, urethral strictures, and squamous cell carcinoma of the anterior urethra with extension into the multiple fistulous tracts of the scrotum

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* Abridged report

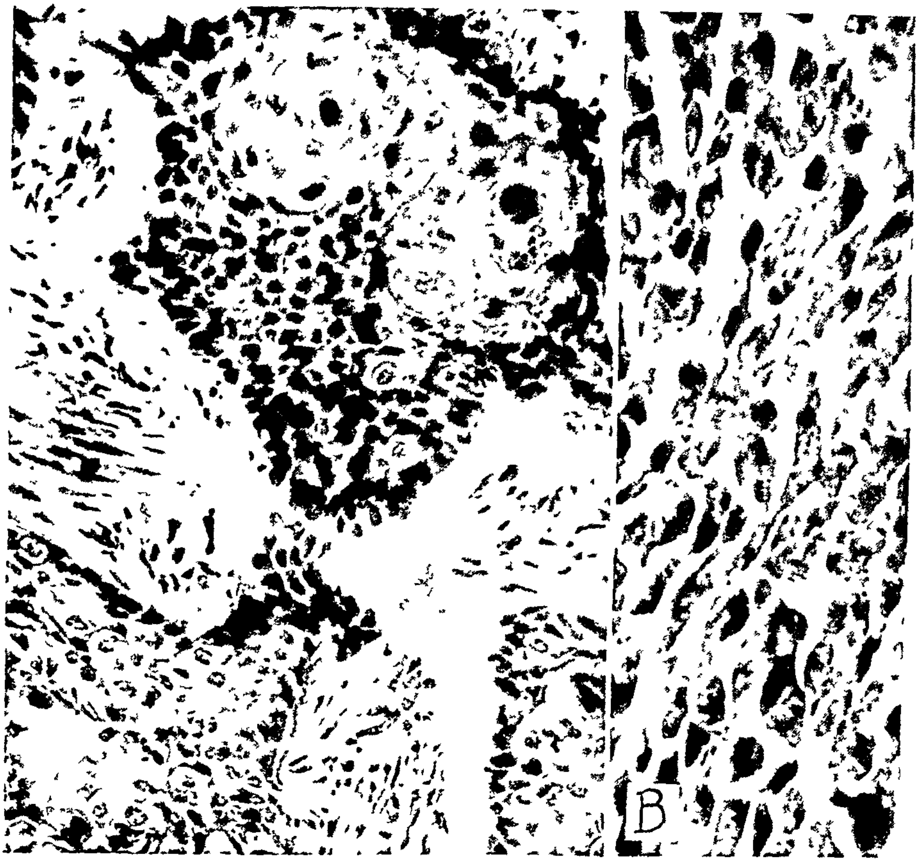

FIG 1. *A*, case 1. Infiltrating squamous cell carcinoma of anterior urethra. *B*, case 10 Anaplastic carcinoma of anterior urethra.

Case 3. W. B., a 41-year old Negro, was admitted to the hospital on March 5, 1947. He complained of dysuria, initial hematuria, and pain in the penis of 3 weeks' duration. He admitted specific urethritis and had received treatment for urethral strictures. The penoscrotal tissues were found to be swollen, indurated and tender but no fluctuation was present. A filiform stricture was found in the bulb of the urethra. The swelling seemed to subside with conservative management but fluctuation developed. An external urethrostomy and incision and drainage of the peri-urethral abscess was performed on March 22, 1947. Pathological report of a biopsy revealed squamous cell carcinoma of the anterior urethra. He refused further surgery at this time but he returned to the hospital 1 month later. A fluctuant scrotal mass and shotty nodules along the perineal urethra were found at this admission. A cystostomy was performed on May 16, 1947. Radical penectomy and left orchiectomy were performed on June 7, 1947. He had an uneventful postoperative course, and he was discharged on the twenty-first postoperative day. Following discharge from the hospital, he left town and no follow-up was possible.

Case 4. N. K., a 55-year old white man, was admitted to the hospital on December 17, 1948. He stated that he had had sounds passed 9 months ago for a urethral stricture. Shortly thereafter a painful perineal swelling developed from

FIG. 2. Case 5. Note local extension of carcinoma to perineum and scrotum

which urine and pus continued to drain. Multiple fistulous tracts were noted in a tender, hard phlegmonous perineum. Biopsy of the fistulous tracts revealed an anaplastic infiltrating squamous cell carcinoma of the anterior urethra. A permanent external urethrostomy was performed on January 29, 1949; the urethrostomy functioned very well. Progressive debility ensued and death occurred on March 26, 1949. The scrotum and perineum had become ulcerated and necrotic.

Case 5. W. K., a 48-year old white man, was admitted to the hospital on May 15, 1949. He complained of pain and swelling of the perineum and voiding through the perineum for 3 months. An abscess in the perineum had been incised and drained at the onset of the disability and the urinary fistulas had persisted. Attempts to dilate the urethra had failed. A large, tender, midline perineal mass with a single fistulous tract was noted in the perineum. Enlarged, firm, discrete lymph nodes were noted in both inguinal regions. Biopsy of an enlarged inguinal lymph gland showed a hornifying squamous cell carcinoma. X-ray therapy was given but the patient died of inanition on September 25, 1949. Figure 2 demonstrates the gross lesion. Autopsy showed a squamous cell carcinoma of the anterior urethra with metastases to the subcutaneous tissue of the lower abdominal wall and the pelvic and abdominal periaortic lymph nodes.

Case 6. J. H., an 80-year old white man, was admitted to the hospital on January 10, 1949. He stated that he had had urethral treatment for a stricture which had followed specific urethritis at the age of 50. Approximately 1 year before admission to the hospital an abscess developed in the scrotum, which followed routine dilatation of the urethra. The abscess was incised and drained. Urine continued to escape from the fistula during voiding and dysuria, initial hematuria, and frequency of urination were present. The scrotum and perineum were indurated and showed multiple urinary fistulas. Both inguinal regions were shotty and indurated. Biopsy of an inguinal lymph node showed transitional cell carcinoma with areas of metaplasia to squamous cell carcinoma. He refused surgery and was discharged in critical condition on January 30, 1949.

Case 7. F. W., a 70-year old white man, was admitted to the hospital on September 22, 1949. He complained of dysuria, nocturia and frequency of several months' duration. He had had pain in the rectum and dribbling of urine for 1 month due to a swelling in the perineum. A urinary fistula was noted in the perineum. It was surrounded by an area of induration. Rectal examination revealed indurated tissue in the anterior rectal wall. Cystoscopy revealed a normal bladder and posterior urethra. Urethroscopy revealed a large necrotic defect in the floor of the bulbous urethra. The irrigating fluid flowed through the perineal fistula. A suprapubic cystostomy was performed on November 15, 1949. The perineal lesion became larger and more necrotic as the patient became more debilitated. He died on March 24, 1950. Postmortem examination revealed an adenocarcinoma of the anterior urethra with invasion of the fistulous tracts of the perineum. Metastases were found in the peri-aortic lymph nodes.

Case 8. A. M., a 63-year old Negro, entered the hospital on February 20, 1950. His history included treatment of urethral strictures for the past 15 years. Two years before admission an external urethrostomy had been performed and a superficial urinary extravasation had been incised and drained. Two weeks before admission to the hospital a perineal and scrotal swelling developed after the urethra had been sounded. A midline perineal mass was noted. The induration extended to the scrotum. Multiple fistulas were present. A suprapubic cystostomy was done on February 28, 1940. Much of the infection and induration subsided after diversion of the urine. On March 21, 1950, the fistulas were resected. The pathological report was squamous cell carcinoma of the anterior urethra. He refused further surgery and was discharged on April 8, 1950. The cystostomy catheter was left in situ. He was again admitted to the hospital on August 14, 1950. Radical penectomy and urethrostomy were performed on September 9, 1950. Histological examination revealed a very anaplastic, hornifying squamous cell carcinoma of the anterior urethra. The wound healed and the postoperative course was uneventful. He was discharged on the thirty-sixth postoperative day. He was admitted to the hospital 6 months later in cardiac decompensation and died 2 days later. There was recurrence of the tumor in the perineum.

Case 9. A. H., a 75-year old Negro, was admitted to the hospital on February 23, 1950. He complained of pain in the penis and perineum of 9 months' duration. Dribbling after urination and hematuria were noted during the past 2 months. An egg-sized perineal swelling was associated with much edema. Multiple fistulas were exuding small amounts of pus. The prostate gland was flat and benign. Urethral calibration failed to reveal strictures. A biopsy of the perineal mass was taken on March 1, 1950, and revealed squamous cell, hornifying and infiltrating carcinoma of the anterior urethra. The urinary stream was diverted by cystostomy on March 11, 1950. His immediate postoperative course was good but his condition deteriorated soon thereafter. He died on March 28, 1950. Autopsy examination was not permitted.

Case 10. T. H., a 36-year old Negro, was admitted to the hospital on Febru-

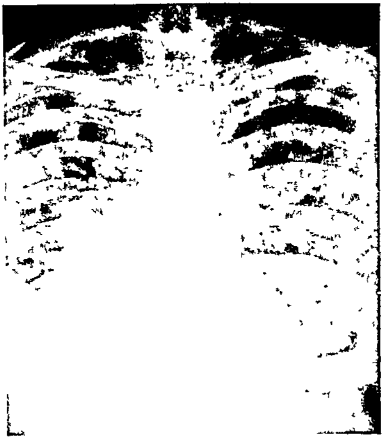

FIG. 3. Case 10. Note pulmonary metastases from carcinoma of anterior urethra

ary 2, 1950. He had received treatment for urethral strictures for the past 7 years. He noted a painful swelling of the perineum 4 months before admission. A spindle-shaped, tender, perineal swelling was noted. The contour was smooth and there was no fluctuation. Biopsy was performed on February 4, 1950. Much polypoid, smooth, glistening tissue was excised. This tissue seemed to encircle the urethra. Pathological examination of the tissue showed very anaplastic, undifferentiated carcinoma of the anterior urethra (fig. 1, *B*). After surgery, the patient's condition failed rapidly and a cough developed associated with blood-tinged sputum. An x-ray film of the chest on February 14, 1950, showed diffuse, nodular infiltration of both lung fields (fig. 3). X-ray therapy was given but the perineal swelling increased in size during the course of treatment. The patient was discharged on April 19, 1950, in a precarious condition.

Case 11. W. R., a 42-year old Negro, was admitted to the hospital on January 15, 1951. He complained of urinary drainage from the scrotum, which had been present for the past 27 years. Ulcers were noted at the margin of the urethral fistula 2 months before admission to the hospital. The ulcers enlarged and showed no tendency to heal. A fungating tumor was noted at the penoscrotal junction. A biopsy of the fistulous lesion showed an infiltrating, anaplastic, hornifying squamous cell carcinoma of the anterior urethra. X-ray therapy was given without demonstrable resolution of the lesion. He became more debilitated and died on July 11, 1951. Figure 4 shows the gross lesion.

Case 12. H. G., a 60-year old white man, was admitted to the hospital on March 17, 1937. He complained of swelling of the left leg and the left groin, which had been present for 3 weeks. Physical examination revealed edema of the left leg and enlarged left inguinal lymph glands. An indurated, grey-pink

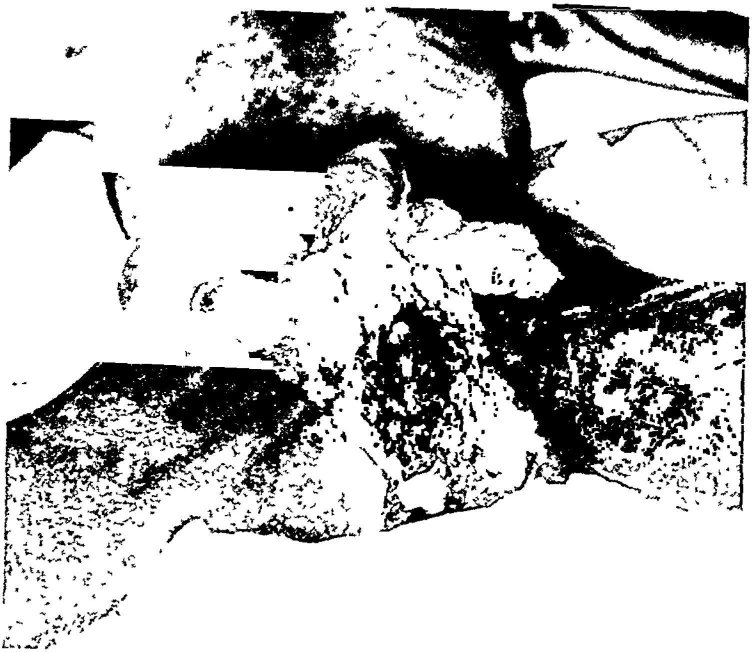

FIG. 4. Case 11. Note local extension of carcinoma of anterior urethra

moist tumor was noted at the external urethral meatus. The distal 1 inch of the urethra was indurated on palpation. Biopsies taken from the urethral meatus and the left inguinal glands revealed a hornifying squamous cell carcinoma of the anterior urethra. The patient expired on April 6, 1937, after a progressively downhill course.

Case 13. W. W., a 61-year old white man, was admitted to the hospital on April 13, 1952. He had received urethral dilatations at intervals for 15 years. The character of the stricture changed 4 months before admission to the hospital. Hematuria and urethral bleeding occurred at intervals although the stricture continued to respond well to sounding. Cysto-urethroscopy revealed only a median prostatic bar. One week before admission to the hospital, the patient noted serous bloody urethrorrhea. Physical examination revealed a swelling which seemed to involve the bulbous and perineal urethra. Calibration of the urethra showed obstruction at the level of the swelling. The prostate gland was small, symmetrical and benign. Abdominal examination was negative. There was no adenopathy. An external urethrostomy was performed on April 15, 1952. Friable tumor tissue and clots were evacuated. A 30F sound was then passed without obstruction. The tumor tissue was found to extend to the membranous urethra. Histopathological study showed masses of atypical epithelial cells with considerable amounts of anaplastic tissue. X-ray therapy was started on April 17, 1952. The urethrostomy catheter was removed on the eighth postoperative day and the patient soon voided with ease per urethram. Examination on June 6, 1952, showed no evidence of recurrence of the tumor and the wound was well healed. A 30F sound was passed without obstruction.

Pertinent facts in the history and findings of these 13 patients have been as-

TABLE 1

	RACE	AGE	PRESENCE OF STRICTURES	HISTOPATHOLOGY
1 J V	W	70	Yes	Squamous cell carcinoma
2 G P	N	64	Yes	Squamous cell carcinoma
3 W B	N	41	Yes	Squamous cell carcinoma
4 N K	W	55	Yes	Squamous cell carcinoma
5 W K	W	48	Yes	Squamous cell carcinoma
6 J H	W	80	Yes	Transitional cell carcinoma
7 F W	W	70	Yes	Adenocarcinoma
8 A M	N	63	Yes	Squamous cell carcinoma
9 A H	N	75	No	Squamous cell carcinoma
10 T H	N	36	Yes	Anaplastic carcinoma
11 W R	N	42	Yes	Squamous cell carcinoma
12 H G	W	60	No	Squamous cell carcinoma
13 W W	W	61	Yes	Anaplastic carcinoma

sembled Strictures of the anterior urethra were found in eleven of the 13 patients (table 1) Strictures were found in 2 patients who denied any history of stricture The urethral tumor may have caused the stricture in those 2 patients The caliber of the strictures varied from filiform to large caliber The patients had had some indefinite treatment of their strictures, but adequate careful attention of the strictures was lacking The constant irritation of the urethra and the metaplasia of the urethral mucosa which is found in the presence of strictures can be ascribed as etiological agents All mention of carcinoma of the male urethra in the literature stresses the high associated incidence of urethral stricture Eighty five per cent of this group of patients were found to have urethral strictures

The predominant pathological lesion was squamous cell carcinoma Nine of the 13 patients were found to have squamous cell carcinoma Transitional cell carcinoma was found in one instance Adenocarcinoma was also found in one instance The origin of the adenocarcinoma cannot be definitely established The glands of Littre, Cowper's gland, or even the prostate gland must be considered The pathogenesis of the lesion seemed to indicate an origin in the anterior urethra Marked anaplasia precluded the classification in two cases This incidence of types of carcinoma corresponds with the previously published series of cases of primary carcinoma of the anterior urethra

One of the patients presented himself with a tumor limited to the distal one inch of the urethra (table 2) All of the remaining 12 tumors originated in the bulbous urethra A simple perineal mass or a chronic perineal urethral phlegmon was noted and the admitting diagnosis was either peri urethral abscess or chronic peri-urethral phlegmon Routine surgical therapy was instituted Biopsy of indurated, cartilaginous tissue was always done A positive biopsy changed the therapeutic approach Radical excision of the lesion and diversion of the urinary stream was feasible in 3 patients Diversion of the urinary stream was performed in three other patients to make them more comfortable No surgical therapy was possible in six of the patients because debility and wasting w

TABLE 2

SITE OF TUMOR	SURGICAL TREATMENT
1. Bulbous urethra	Cystostomy and emasculation
2. Bulbous urethra	None
3. Bulbous urethra	Cystostomy and penectomy
4. Bulbous urethra	Urethrostomy
5. Bulbous urethra	None
6. Bulbous urethra	None
7. Bulbous urethra	Cystostomy
8. Bulbous urethra	Urethrostomy and penectomy
9. Bulbous urethra	Cystostomy
10. Bulbous urethra	None
11. Bulbous urethra	None
12. Distal urethra	None
13. Bulbous urethra	Urethrostomy

TABLE 3

DURATION OF SYMPTOMS	INTERVAL BETWEEN DIAGNOSIS AND DEATH	LOCATION OF METASTASES	AUTOPSY
1. 5 mos.	1 mo.	Scrotum and perineum	No
2. 4 mos.	1 mo.	Scrotum and perineum	Yes
3. 3 wks.	Unknown	Scortum and perineum	No
4. 9 mos.	3 mos.	Scrotum and perineum	No
5. 3 mos.	6 mos.	Perineum, inguinal and periaortic nodes	Yes
6. 1 yr.	1 mo.	Scrotum, perineum and inguinal nodes	No
7. 1 mo.	6 mos.	Scrotum, perineum and periaortic nodes	Yes
8. 2 wks.	6 mos.	Scrotum and perineum	No
9. 9 mos.	1 mo.	Perineum	No
10. 4 mos.	3 mos.	Lungs and perineum	No
11. 2 mos.	6 mos.	Scrotum and perineum	No
12. 3 wks.	1 mo.	Inguinal nodes	No
13. 4 mos.	Living	None evident	—

marked at the time of admission to the hospital. The most recent patient was treated by urethrostomy and evacuation and excision of all easily available tumor tissue. The degree of extension of the tumor seemed to preclude a cure by radical excision and diversion of the urinary stream. Massive postoperative x-ray therapy was given and the wound healed very well.

Most of the patients had tolerated their complicated disease states for months before desperation drove them to the hospital for relief (table 3). The carcinomas had extended locally and distantly during the delay. Definitive surgery was possible in only three of the patients. One of these patients, case 1, died 3 days after surgery in peripheral collapse. A second of the 3 patients, case 8, died 6 months later in cardiac failure. He had evidence of recurrence. The third of the 3 patients, case 3, was inconsistent in returning for examination and his clinical

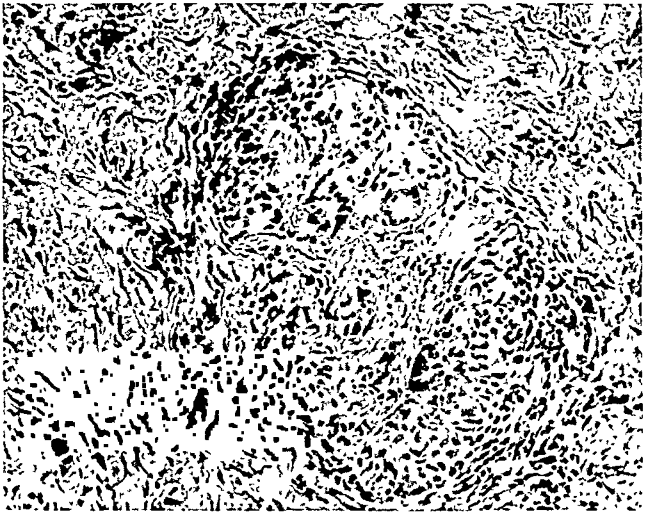

FIG. 5. Tuberculosis in tissues of perineal sinuses

result is unknown. None of the patients who were followed were alive 6 months after the diagnosis was established. Local metastases to the perineum and scrotum were noted in all of the advanced lesions of the bulbous urethra. The lesion which was limited to the distal urethra had a proven metastatic lesion of an inguinal gland. Distant metastases were found in five of the 13 patients. The inguinal nodes were the most common site of distant metastases.

The therapeutic results in these patients have been exactly what one would expect when the carcinoma had progressed to an advanced stage. Better results depend upon earlier diagnosis. Metastases were present in all of these advanced lesions.

The differential diagnosis must include tuberculosis. A recent patient came to the attention of the authors. E. M., aged 73, a white married man, was admitted to the hospital on June 25, 1951. Physical examination revealed multiple perineal fistulas through which infected urine was passed. The fistulas had been present for 2 years after the spontaneous rupture of a perineal abscess. The perineum was indurated and a mass was found to involve the bulbous portion of the urethra. On July 26, 1951, the fistulas were dissected and excised, and the tumorous, indurated urethral bulb was exposed. A frozen section biopsy was reported as inflammatory tissue. An external urethrotomy was performed and the anterior urethra was dilated to size 28F. The urethrostomy catheter was removed on the fifth postoperative day. Sounds were passed through the urethra on the tenth day. Streptomycin therapy was started when the routine histologic study revealed tissues which resembled tuberculous granulations. The urethrostomy healed and sounds were easily passed (fig. 5).

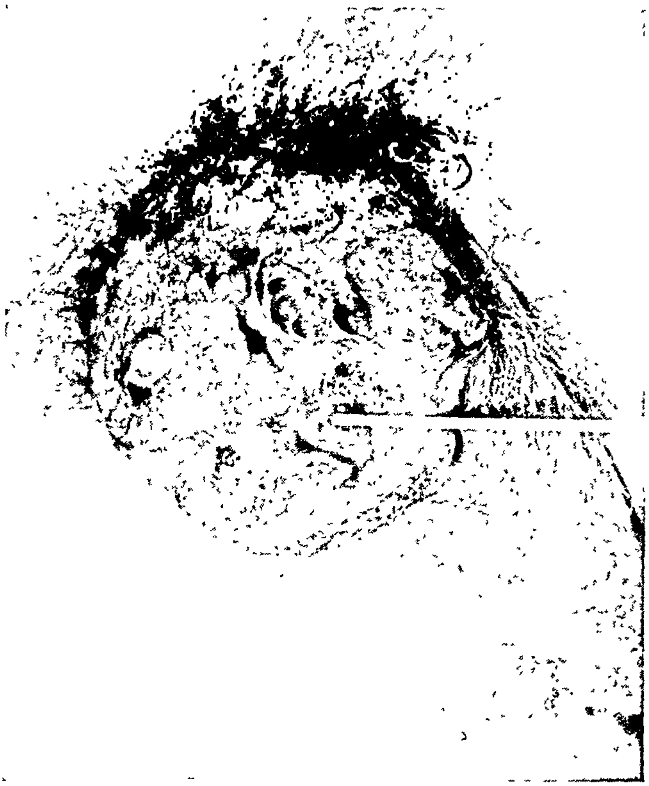

FIG. 6. Gumma of penis. Pointer indicates urethral stump

Figure 6 demonstrated a gumma of the penis which must also be differentiated from carcinoma of the urethra.

DISCUSSION

The patients who have been presented are representative of the final stages of carcinoma of the urethra. The symptoms of early carcinoma of the urethra, such as blood-tinged urethrorrhea, diminution of the urinary stream, and hematuria were either disregarded or not noted. These patients neglected the care of the urethral strictures. Changes in the character of the strictures which are suggestive of carcinomatous metaplasia were observed in only 1 patient. This particular patient was the only one of this series of patients who was from private practice.

Authors who have written about carcinoma of the anterior urethra stress the importance of two factors in the early diagnosis. The sudden onset of difficult sounding of a urethral stricture, which had previously responded well to therapy, should arouse suspicion of carcinoma. The second factor is the more frequent use of urethroscopy. Urethroscopy should not be delayed until a mass or induration is palpable along the urethra. Papillomatous tumors which present at the urethral meatus afford no difficulty in early diagnosis.

SUMMARY

Thirteen instances of primary carcinoma of the anterior male urethra are reported. Twelve of the 13 patients were treated initially as peri-urethral abscess and peri-urethral phlegmon The diagnosis of carcinoma of the urethra was established after histopathological study of biopsy specimens It is our impression that the true incidence of carcinoma of the urethra will become more obvious as more biopsies of urethral and peri-urethral disease are studied Realization of the true incidence will be a potent influence to search for early phases of carcinoma of the urethra

7 W Madison St , Chicago 2, Ill

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PSEUDODIPHALLIA, A RARE ANOMALY

XAVIER VILANOVA AND ANTONIO RAVENTOS

From the Dermatological Clinic of the University of Barcelona, Spain

It may be that in adults a double penis, owing to the psychological complex which it produces in those affected with it, causes the patient to conceal his deformity instead of seeing a physician, which fact proves detrimental to the statistics showing the actual frequency of this malformation and not only with regard to its actual incidence, but also with a view to its comparison with other congenital and plainly visible anomalies (harelip, congenital dislocation of the hip, etc.). Notwithstanding the aforementioned circumstances, its incidence must be slight, since, on the one hand, there are cases of double penis which, owing to the fact that they coincide with an exstrophy of the bladder or another important malformation, have to be seen by a physician, while, on the other hand, as is frequently the case, the coincidence of their appearance in foetus or newborn or little boys, whose desire to prevent their deformity from becoming known does not carry any weight, leads one to believe that there are very few cases which remain unrecognized. All this makes the case which we are about to report very interesting, while its correct interpretation is rendered extremely difficult by its unusualness, the age at which it was observed and its clinical, topographical and histological features.

HISTORICAL DATA AND REVIEW OF THE LITERATURE

In 1898, Neugebauer[1] published the most comprehensive review up to that date of all known cases of double penis which, including his own, amounted to 28 cases. According to him, it was J. J. Wecker who published the first case in 1609, two more cases being encountered during the same century, five during the eighteenth and 21 as well as a personal case during the nineteenth centuries.

In 1933, Nesbit and Bromme[2] published a new review, based on Neugebauer's study, to which 16 further cases, including a personal one, were added. This review is, however, incomplete, as a considerable number of cases of other authors, which have remained unnoticed, are lacking.

In chronological order the following cases were published prior to the study of Nesbit and Bromme and not mentioned by them: Pires de Lima,[3] Lipschütz,[4] Corrado,[5] Behdjet Sabit Erduran,[6] Thomson,[7] Donald,[8] Bauzá,[9] Palieri,[10] De

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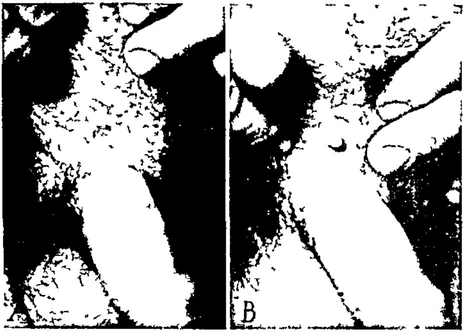

FIG 1 *A*, appearance of alopecic area with umbilicated nipple (with central orifice) beneath which pseudopenis is concealed (above is root of normal penis) *B*, appearance of pseudopenis prolapsing as result of pressure on neighboring regions

Gaetani,[11] Phillips,[12] Sloboziano, Georgescu and Floru,[13] Cochrane and Saunders,[14] Blanco,[15] Acevedo Ruiz del Hoyo y Blanco,[16] Davis,[17] Pendino,[18] Solomon [19]

CASE REPORT

J. Alonso G., 30 years of age, unmarried, was a railway worker by occupation. Neither his personal history nor that of his family showed any important features. None of his relatives had presented any malformation to his knowledge. A few years ago he noticed a scab in the pubic region, right over the root of the penis, which was shed of itself, a small nipple-like elevation, the size of a pea, appearing beneath it, which discharged a whitish, sticky secretion (compared by the patient to that of the nocturnal pollutions), which had continued When he had not urinated for several hours and had a full bladder, he observed a feeling of tension in this region, which did not become painful

In the pubic region and above the root of the penis a circular area, 5 cm in diameter, alopecic and therefore deprived of hair, was observed, with a nipple-like elevation at the centre (fig 1, *A*), which showed a more pronounced prolapse when pressure was exerted upon the surrounding skin, rising to a height of about 14 mm. and vaguely resembling an abnormally developed mammary nipple, which was perforated at its apex and which discharged a minute quantity of transparent, mucous secretion on expression (fig 1, *B*) It was completely ensheathed by a delicate, pink-white membrane, covering its cylindrical surface, which had a small diameter (7 mm), while the vertex of its distal portion showed an orifice, through which a filiform bougie could be inserted up to a depth of about 2 cm. The patient stated that the alopecic zone surrounding this nipple became a zone of erotic excitation when stimulated with the fingers, or even on simple contact with the clothing, which sensation, on the other hand, failed to appear either spontaneously or when coitus was carried out with the normal penis. The scrotum and testes, as well as the penis, were normal, without dicrotism or hypospadias. The functional condition of the bladder was also normal. An examination by rectal touch showed the prostate and seminal vesicles to be normal. Neither the anus nor the rectum showed any change.

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Excretory urography revealed the presence of two normal kidneys, somewhat descended and rotated (possibly as a result of the compression required by the radiogram, with a slightly dilated pelvis and two normal ureters as well as a normal bladder. Neither the lumbosacral region of the spinal column nor the pubis showed any abnormality.

Operation (January 24, 1950): Under local anesthesia (1 per cent novocain block) oval excision of the skin was made around the prolapsing pseudopenis in the bald region following previous catheterization of the duct, which was dissected. At about 2 cm. under the surface of the skin the dissection revealed a hard cord which penetrated deeply among the rectus and pyramidalis muscles and which also ran backward above the symphysis pubis, to be inserted in the apex of the bladder. At this site it was ligated and cut, so that the entire piece could be removed. Suture of the muscles was done and also the skin, which healed by first intention within 7 days.

Since then the patient felt quite well, except that, as had previously been the case, whenever he refrained from urinating for an excessively long period and the bladder became subject to tension, he experienced a feeling of heaviness in the pubic region. The erotic feeling, produced in the alopecic suprapubic region by contact, had disappeared. The urogenital functions showed a normal development.

Histological examination of the specimen (figs. 2, 3 and 4): The specimen obtained by surgical extirpation was divided into four portions by cross section at 5, 10, 15 and 20 mm. from its free end. The first three portions represented cross sections of the nipple which could be exteriorized by lateral pressure in the suprapubic alopecic area presented by the patient. The fourth portion corresponded with the first part of the fibrous cord which the operation, on removal of the supposedly rudimentary penis, had shown to insert with the apex of the urinary bladder.

The histological specimens corresponding with the first section (fig. 2) showed a large central cavity with an irregular stellate shape, lined with polystratified epithelium of a malpighian type and consisting of a row of basal cells, numerous layers of superposed prickle cells, a granulosa supplemented by a single cellular layer and a slender, though manifest, horny coating. We found this structure to be surrounded by a fibrous chorion, which showed a few vaguely outlined papillae, whereupon it continued and merged into a strong, also very thick and concentrically arranged casing, at the periphery of which smooth muscle fibres

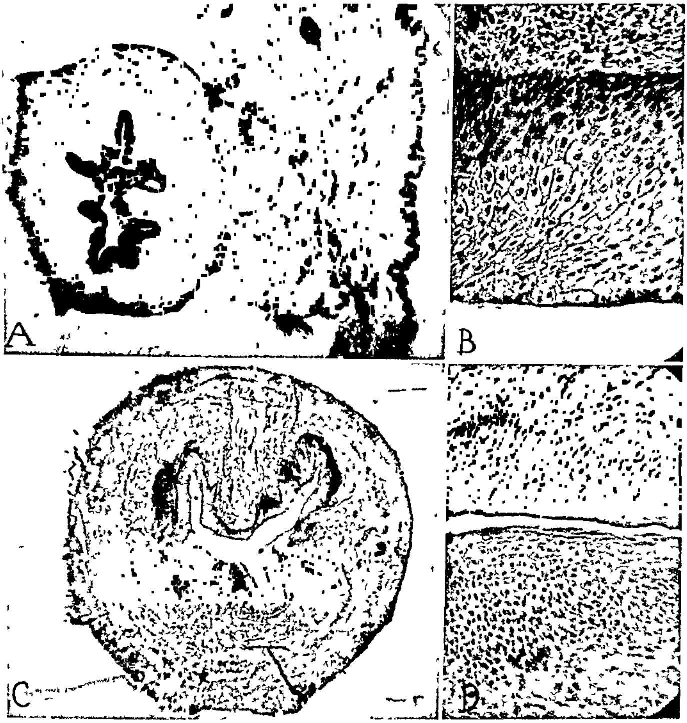

Fig. 2. *A*, cross section of piece excised at 0 5 cm. from its distal end Central duct is bounded by malpighian type of epidermis with granulosa layer of only one row At periphery it is surrounded by thick sheath of fibrous connective tissue, which is seen to contain bundles of smooth muscle fibers, arranged in longitudinal and circular pattern This sheath continues in loose connective tissue present in deep layers of skin which, covered by cutaneous type of epidermis, [illegible] *B*, detail of central duct of excised specimen reproduced [illegible] helium *C*, cross section of piece excised at 1 cm. from dis[illegible] of semimembranous mucous type with preservation of nucl[illegible] and with tendency to protoplasmic vacuolation. Peripherally there is same sheath of fibrous connective tissue, with muscle fibers described in *A* and *B*, but larger in size. Chronic common infiltrations in superficial chorion *D*, detail of central duct of excised specimen reproduced in figure 1, *B*. Epithelium of semimembranous mucous type.

were well in evidence, some showing a longitudinal and others a transverse pattern. There were no vascular angiomatous formations. There was a considerable framework of elastic tissue. The skin which covered this new growth did not present any changes and merged into it in the deeper part of the chorion, no adipose tissue being interposed between the skin and the growth.

The sections carried out at a deeper level, i.e. at 10 mm. from the surface of

be compared with that of the semimucosa of the mouth and the fossa navicularis of the meatus On the other hand, the corium was provided with numerous papillae The papillary body was slender and presented common, though considerable inflammatory infiltrations Below this papillary body we encountered the thick and sclerous connective tissue which surrounded the central cavity, with its scarce and hardly visible transverse and longitudinal bundles of smooth muscle The extensive network of elastic tissue continued The form, dimensions and structure of the central canal showed a radical change when it was examined at 15 millimeters from the surface of the skin (fig 3) The cavity no longer showed a stellate form, but was regularly circular The bordering epithelium continued to be polystratified, though presenting a cylindrical type At the surface there was a layer of cylindrical cells, with three or four rows of cuboid cells underneath There was a flaccid and infiltrated papillary body, though less than in the sections of the anterior segment, but this papillary body did not penetrate into the epithelial layer so as to form true papillae The covering sheath of fibrous connective tissue still persisted, though it was smaller in size, it continued to show an equally large quantity of muscle fibres and it still lacked any angiomatous vascular formations At a depth of 20 mm we finally identified the apparently fibrous composition of the cord, which inserted with the apex of the urinary bladder (fig 4)

Still centered by a very small and considerably reduced cavity with an irregular outline, which was still permeable in the sections that were studied, the bordering epithelium had been reduced to two or three layers of flattened cells, which were suggestive of the transitional type of epithelium between the prostatic urethra and the urinary bladder The casing of fibrous connective tissue which we had traced from the surface up to this point continued to surround it though it had been considerably reduced and was far less marked, nevertheless its more peripheral portions still showed some longitudinal and transverse patterns of smooth muscle fiber

COMMENT

With the cases available to him, Schneider[20] attempted to class the various forms of double penis according to three groups. 1) diphallia of the glans alone, 2) bifid diphallia and 3) complete diphallia or double penis To this scheme we must add those forms which might be termed pseudodiphallia or at any rate those cases in which a normal or almost normal penis is associated with an indication or rudiment of an atrophic penis, existing independently of the normal penis It goes without saying that even the more complete malformations, such as double penis, also present variations of the incomplete stages, like, for instance, the hypospadiac meatus or the blind urethra or the presence of a perineal hypospadias, while in both penes there is no permeable urethra etc In addition to this systematic confusion, diphallia frequently coincides with other malformations which complicate its classification and which may be found in the urinary and genital tract, the digestive system, the vertebral column, the extremities. Naturally the malformations associated with diphallia are frequently incompatible with a prolonged duration of life, which is the reason that there is such a small number of adults with double penis. Finally a general physical examination as well as an investigation of the psychosomatic factor, which the patient has to bear as a result of his malformation, is indispensable.

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[20] Schneider Handbuch der Urologie Lichtenberg, Voelcker and Wildbolz *III* Berlin Springer, 1928, p 160

A review of the literature, which was complete as far as double penis was concerned, failed to reveal any cases among those published and studied which were comparable with ours. The absence of cavernous tissue as well as the form and structure of the supposed supernumerary penis, without glans, compel us to have some reserves with regard to the organoplastic significance to be attributed to the appendix presented by our patient. There are good reasons in support of a diphallia, such as the presence of well developed smooth muscle fibers, running in a longitudinal and transverse direction in the region of the outer layers of the casing of fibrous connective tissue surrounding the central duct, lined with a polystratified epithelium like the fossa navicularis around its central orifice and of a polystratified cylindrical type, similar to that of the membranous urethra, more profoundly and conclusively simulating that of the prostatic urethra in its union with the urinary bladder, at a greater depth. The large quantity of elastic fibers in the submucosa and the erotic zone localized in the alopecic area surrounding its opening in the skin are also facts which should be taken into account. One should also consider the question as to whether it constitutes a permeable urachus, while particularly taking into account the fact that the operation shows the fibrous cord following the supposed rudimentary penis to be inserted in the depth at the level of the anterior surface of the urinary bladder below the vertex vesicae.

Nevertheless, having among other things, carefully examined Cullen's book[21] and the studies of Dudgeon,[22] Trimingham and McDonald,[23] Williams[24] and Garvin,[25] in which the cases of persistence of a permeable urachus are studied in detail, we have not been able to find a single case among those quoted, in which this canal or a diverticulum of it opened into the skin at the pubic region, as in our case, since in all these cases the opening was in the umbilical region, a logical and inevitable fact, considering the embryonic development.

Lannelongue's case[26] does not deviate from the aforementioned rule and thus we see how the urinary fistula presented by his little patient, and by means of which he was able to urinate through an orifice lined with a mucosa which caused it to simulate a normal meatus, established on a cutaneous stump from which a granuloma emerged, opened into the umbilical region.

On the other hand, as Vaughn[27] says, cases of patent urachus usually only cause fistulas in the umbilical region (completely permeable or externally blind, or permeable in the juxtavesical region) or closed at both ends and thus giving rise to an urachal cyst

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[21] Cullen, T. S.: The Umbilicus and its Diseases. Philadelphia: W. B. Saunders Co., 1916.

[22] Dudgeon, H. Jr.: Surg. Gynec. & Obst., **71:** 302, 1940.

[23] Trimingham, J. L. and McDonald, J. R.: Surg. Gynec. & Obst., **80:** 152, 1945.

[24] Williams, C.: Ann. Surg., **124:** 1110, 1946.

[25] Garvin, E. G.: Patent urachus, J. Internat. Coll. Surg., **11:** 511, 1948.

[26] Lannelongue: Quoted by the Encyclopédie Med.-Chirurgicale. vol. 2. no. 2008, p. 3.

[27] Vaughn, G. T.: Patent urachus. Trans. Amer. Surg. Assoc., **23:** 273, 1905.

And Garvin's case[25] is only curious because of the fact that, even though the urachus opened into the umbilicus, the patient also presented a very delicate and shining patch of skin in the pubic region, similar to that encountered in exstrophy of the bladder

Nor do the hypotheses advanced in explanation of these malformations have any value for a correct interpretation of the deformity presented by our patient Those theories which tend to attribute these malformations to a hypothetical atavism (double external genitals as in lizards and snakes) are not based on solid facts, nor is this the case with those hypotheses, according to which they should be considered as teratoid structures or as the lowest stage of a duplication

At present one would appear more correct in assuming them to be due to a disturbance in embryonic development occurring at the moment in which the mesodermal cellular mass, which lies between the two layers of epithelium (the ectoderm on the outside and the entoderm on the inside) of the cloacal membrane, does not only give rise to all the mesodermal structures of the lower abdominal wall, but also to the genital tubercle The bilateral development of this tubercle and of its pillars clearly explains how the failure of these formations to fuse or any interference with their normal development at this point (anlagen) may bring about a condition of double penis

Its frequent co existence with other malformations suggests that the concept of a developmental disturbance is a correct one, which disturbance is, as in so many other cases, attributed to syphilis, an unproven fact, the detection of which by a hereditary taint or by a positive serological test fails in a great number of cases, as it did in ours

Thus, incapable of interpreting and therefore of definitely classifying our patient's malformation, we have labelled it penile pseudodiphallia, which term in no way prejudices its ultimate designation and which we have only found to be previously used by English[28] and Acevedo Ruiz del Hoyo and Blanco Castillo[16] in a publication which we were unable to obtain

SUMMARY

Only a few cases of double penis and pseudodiphallia have been publ[illegible] the medical literature We have reported a case of pseudodiphallia wh[illegible] cording to the review of the literature, is the sixty second case of this [illegible] malformation

We have classified the deformity presented by our patient as pseudo[illegible] because in this case the supernumerary penis only consisted in the ur[illegible] rounded by a chorion of muscle and connective tissue, though wi[illegible] traces of corpora cavernosa or of a bulb We have, moreover, per[illegible] belief that this case was one of pseudopenis, as its localization and [illegible] of the duct were suprapubic, far from the umbilical region, and [illegible] the mucosa lining the central canal of the nipple presented, from [illegible]

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[28] English Quoted by Blanco Castillo [15]

the bottom and as far as its epithelial constituent was concerned, a structure similar to that shown by a normal urethra considered in its various branches from the meatus to the urinary bladder, so that this structure cannot be mistaken for an abnormal persistence of the urachus. Both a physical examination and descending urography failed to reveal any other anomaly of the genitourinary tract in this patient. Also the alopecic area in the skin surrounding the prolapsing orifice of the supernumerary penis, as well as the erotic feeling produced by a mechanical stimulation of this region, should be considered to support our claim.

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RADICAL RETROPUBIC PROSTATECTOMY FOR CANCER

RICHARD CHUTE

Next to carcinoma of the stomach, carcinoma of the prostate is the most common cancer in the male, and over the age of 60 it is the most common cancer in men.

Rich[1] of Johns Hopkins, Moore[2] of Cornell, Kahler[3] of the Mayo Clinic, and Baron and Angrist[4] of Queen's General Hospital, Jamaica, N. Y., working quite independently of each other, carefully examined prostates at autopsy in a combined total of 1,276 unselected patients who had died from a variety of causes. They found an incidence of carcinoma of the prostate in men over 50 of from 14 per cent to 46 per cent, making a general average of 24 per cent—or one man out of almost every four. In most cases the cancer was small, had not spread beyond the capsule of the gland or metastasized, and had nothing to do with the patient's death—and also had not been diagnosed clinically.

In 1900 the expectancy of life in the U. S. was 47 years, whereas in 1947 it had risen to 67 years. This means an increasing number of men in the prostatic age living. According to the Bureau of the Census, as of April 1, 1950, there were more than 16 million men in this country 50 years of age and over. Therefore, based on the figures of the investigators, it is estimated that there are at least 2⅓ million, and possibly as many as 7½ million men in this age group, afflicted with carcinoma of the prostate today. Hinman[5, 6] has estimated that only 5 per cent of patients with carcinoma of the prostate are seen early enough to be suitable for radical prostatectomy. However, my own personal experiences have been more favorable than this, and would incline part way in the direction of Colston's[7] figure of about 20 per cent of cases being suitable. If, for the sake of the argument, we accept Hinman's low figure and also the average figure of incidence of 24 per cent of the four investigators already mentioned, there are today at least 195,000 men of 50 or over in the United States with carcinoma of the prostate in a stage early enough to be probably curable by surgery. If we accept Colston's figure and the highest figure of the investigators, there are 1½ million men over 50 with prostatic carcinoma probably curable by surgery.

Although these figures mean that carcinoma of the prostate is extremely common, the investigations of the foregoing—and of other workers also indicate that this disease usually is slow growing and slow to spread beyond the capsule of the gland or to metastasize. Also, it has been found that no matter in what part

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Read at annual meeting, South Central Section, American Urological Association, Hot Springs, Ark. September 30, 1952.

Note by editor. A more extensive discussion of the subject will be found in the Transactions of the South Central Section 1952, pp. 51-80.

[1] Rich, A. R. J. Urol. 33: 215-223, 1935.

[2] Moore, R. A. J. Urol., 33: 224-234, 1935.

[3] Kahler, J. E. J. Urol., 41: 557-574, 1939.

[4] Baron, E. and Angrist, A. Arch. Path., 32: 787-793, 1941.

[5] Hinman, Frank. J. A. M. A., 135: 136-141, 1947.

[6] Hinman, Frank, Jr. Calif. Med., 68: 338-343, 1948.

Colston, J. A. C. J. A. M. A., 127: 69-74, 1945.

1.

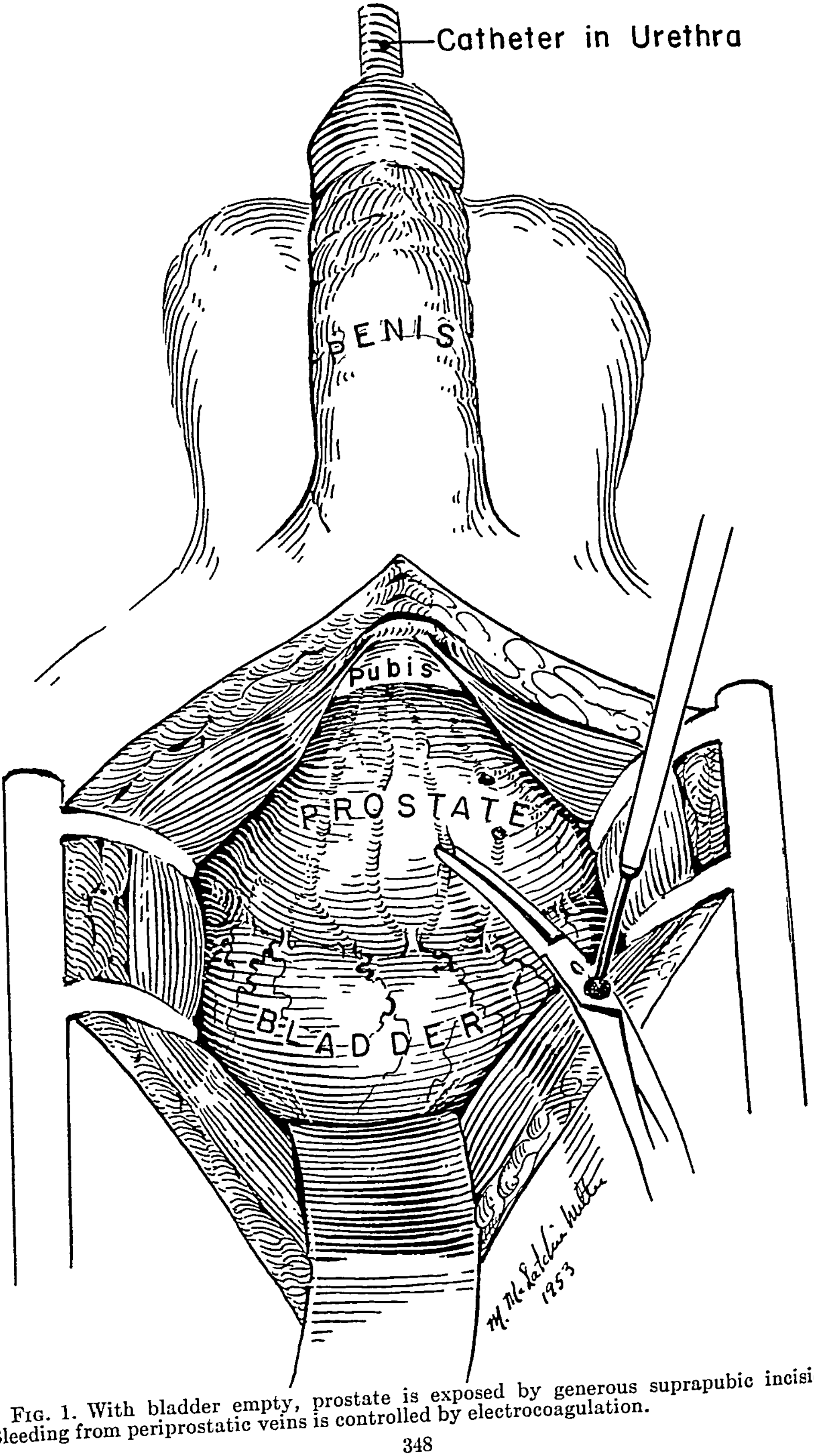

FIG. 1. With bladder empty, prostate is exposed by generous suprapubic incision. Bleeding from periprostatic veins is controlled by electrocoagulation.

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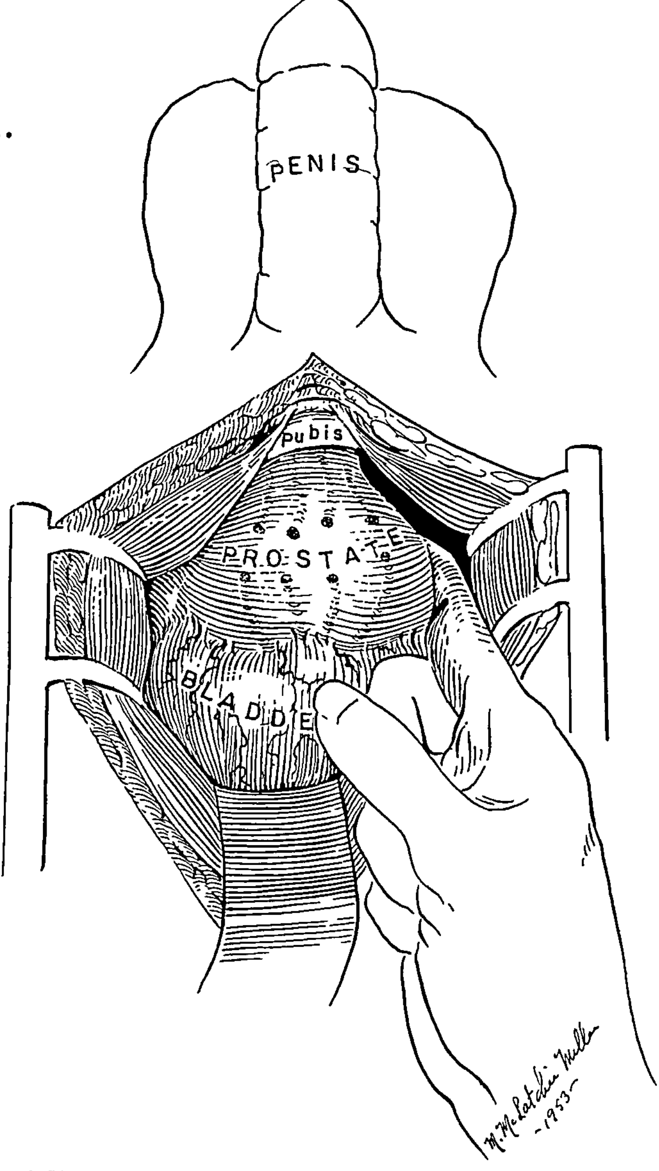

FIG. 2. Finger has broken through endopelvic fascia on right side of prostate, and is now bluntly but gently working forward in a good cleavage plane toward membranous urethra. Same procedure will be carried out on other side of prostate.

of the gland the disease originates, it almost always spreads within its confining capsule at first, so that the posterior or lateral portions, in which hard areas or irregular nodules can be readily palpated by the examining finger, become involved before the cancer breaks out through the barrier of the capsule and starts to spread and to metastasize. Such a type of tumor should be particularly amenable to cure by radical surgery, if detected in time. And indeed this has proven to be so, for in such cases Young,[8] Colston,[7] Hinman,[5, 6] and Jewett[9] have obtained 44–51 per cent of 5-year cures, without detectable recurrence or metastasis, by means of radical perineal prostatectomy. These results are definitely superior to the 43 per cent of 5-year survivals, but with disease still present, obtained by orchiectomy and/or estrogenic therapy in patients without metastases when first seen, reported in the large-scale survey made by Nesbit and Baum.[10] Thus, as a rule, every case of cancer of the prostate goes through a stage when the disease is still confined inside the capsule, where it can be successfully detected by rectal palpation, and when it is usually curable by radical prostatectomy.

Why then is not the general rate of cure of cases of carcinoma of the prostate throughout the country higher than it is, and why is the general attitude toward this lesion one of extreme pessimism and defeatism? There are two principal reasons for this. The first is that very frequently cancer of the prostate grows so silently and asymptomatically that, by the time it produces symptoms bothersome enough to cause the patient to consult a physician, it has already spread too far to be removed surgically—and very possibly has also metastasized. One accessory factor possibly contributing to this "missing the boat" is the fact that, since the first symptoms of cancer of the prostate are often identical with the well-known ones of benign prostatic hypertrophy—i.e. nocturia, frequency, and slowness of urination—many elderly men regard such symptoms as normal prostatic accompaniments of advancing age, and therefore unfortunately postpone consulting their doctor for months or even years until these symptoms finally become so bothersome that they reluctantly resign themselves to the dreaded "prostate operation" and at last seek medical aid. An educational program to counteract this lag between the time urinary symptoms appear and the time the physician is consulted would save many lives through the earlier detection of malignancy, not only of the prostate but also of the bladder. An equally important educational program—which is starting to make some progress in general acceptance—is that of the annual physical check-up, including rectal examination, and also for physicians to routinely examine the prostate of every male patient over 50 who consults them—no matter for what reason. In this way many asymptomatic early prostatic cancers have been discovered in the past, and many more will be discovered in the future.

The second reason why the general rate of cure of cancer of the prostate throughout the country is not higher is that radical prostatectomy is now not performed on many early operable cases, even though the disease has been detected The explanation for this is that, although radical perineal prostatectomy, the only operation available for total prostatectomy until the recent advent of the radical retropubic operation, has been known for nearly 50 years (Dr Hugh Young did his first case in 1904), and despite the previously quoted figures showing its favorable cure rate, many urologists just will not perform this operation Probably this is because comparatively few urologists have been trained in the centers where radical perineal surgery is practiced and, feeling insecure in the depths of the perineum, and realizing that a mis step may mean incontinence or a recto urethral fistula (which occasionally occurs in even the most expert hands), they elect to leave the somewhat exacting operation of radical perineal prostatectomy strictly alone, preferring the several years of palliation usually guaranteed by riskless hormonal therapy (with or without transurethral resection as indicated) to the risks of incontinence or fistula entailed in the attempt—sometimes unsuccessful—to obtain a complete cure by radical perineal surgery Thus it is that hundreds or perhaps thousands of men every year who could very probably be cured by radical prostatic surgery have their chance of cure denied them and are condemned to eventual death by receiving the inferior substitute of hormonal therapy which is palliative only

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[8] Young, H. H.: J. Urol., **53**: 188–252, 1945.
[9] Jewett, H. J.: J. Urol., **61**: 277–280, 1949.
[10] Nesbit, R. M. and Baum, W. C.: J.A.M.A., **143**: 1317–1320, 1950.

Fortunately for this sorry situation, the recently developed radical retropubic prostatectomy now provides an alternative procedure for radical prostatectomy which is not only as satisfactory as the radical perineal, but which may very well turn out to be a better operation The anatomy is less complicated than in the perineal approach, and the incision gives better access to the important deeper structures such as the region of the tips of the seminal vesicles, with the result that the operation is easier to perform By it, not only can the prostate in its capsule en bloc with the seminal vesicles be removed as completely as via the perineal route, but actually it is easier to remove plenty of the crucial tissue around the seminal vesicles, making for a better cancer operation There is definitely less chance of injuring the rectum, which is borne out by the record Furthermore it allows for abdominal exploration, and for dissection of the pelvic lymph nodes, should these procedures, impossible via the perineal route, be desired or indicated If extraprostatic local spread were found, the injection of colloidal radio active gold, as described by Flocks,[11] could be carried out in conjunction with it

Radical perineal prostatectomy was introduced originally by Millin of London[12] and by Memmelaar of Bangor, Maine,[13] and also has been practiced by Flocks of Iowa City, Atherton of Louisville, Kentucky, Hand of Portland, Oregon, as well as by many others, and is gaining increasingly favorable recognition

Although I personally have used radical perineal prostatectomy for years in all my cases of operable prostatic carcinoma, I recently decided to give the radical retropubic a trial While I have done this operation in only a small series of cases, the excellent impression which it has made has prompted me to recommend it for total prostatectomy

[11] Flocks, R H , Kerr, H D Elkins, H B and Culp D J Urol , 68 510–522, 1952

[12] Millin, Terence Retropubic Urinary Surgery Baltimore Williams & Wilkins Co , 1947

[13] Memmelaar, J J Urol , 62 340–348, 1949

3.

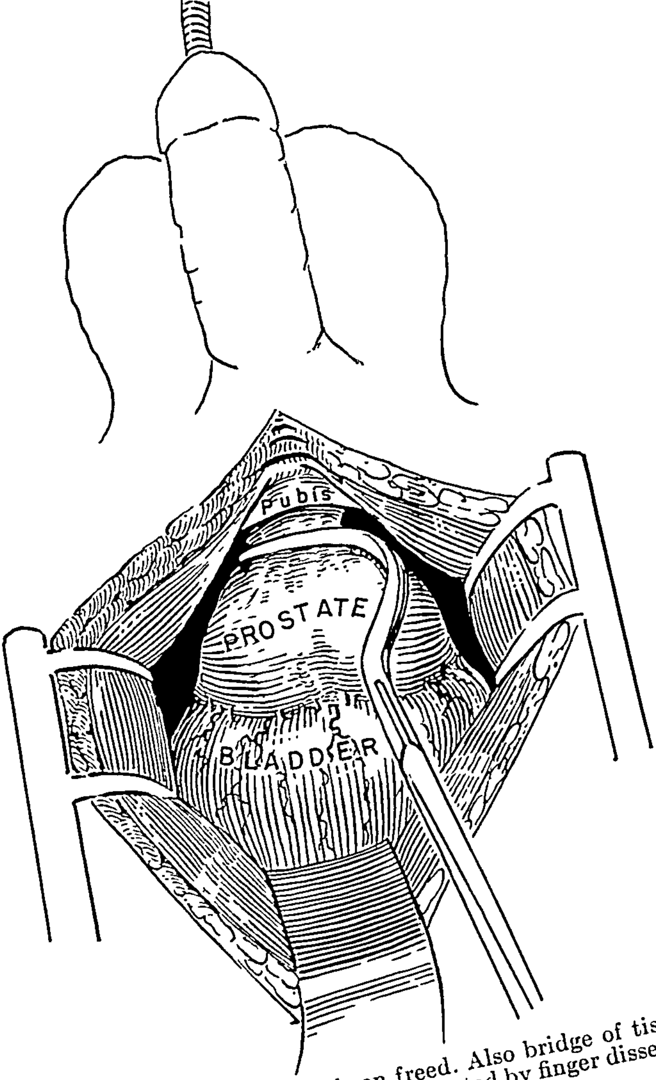

FIG. 3. Both sides of prostate have been freed. Also bridge of tissue containing puboprostatic ligaments and large veins has been separated by finger dissection from underlying membranous urethra, and is now being clamped.

Since my own series of cases is small, and the follow-up period too short to be significant, I believed that my presentation would be more valuable if I added to it the observations of four of those who have had the widest experience with the operation. Consequently in the summer of 1952 I contacted, either in person or by mail, Mr. Millin and Doctors Memmelaar, Flocks, and Atherton, who very generously made their data available to me. All of these men, with one exception, had done upwards of fifty cases, and Doctor Atherton had done more than twenty cases. Also these men had done this operation in some additional cases which turned out not to be malignant, so that the total experience represented, including my own cases, amounted to more than two hundred of these operations.

Let us now examine some of the more important questions concerning this operation.

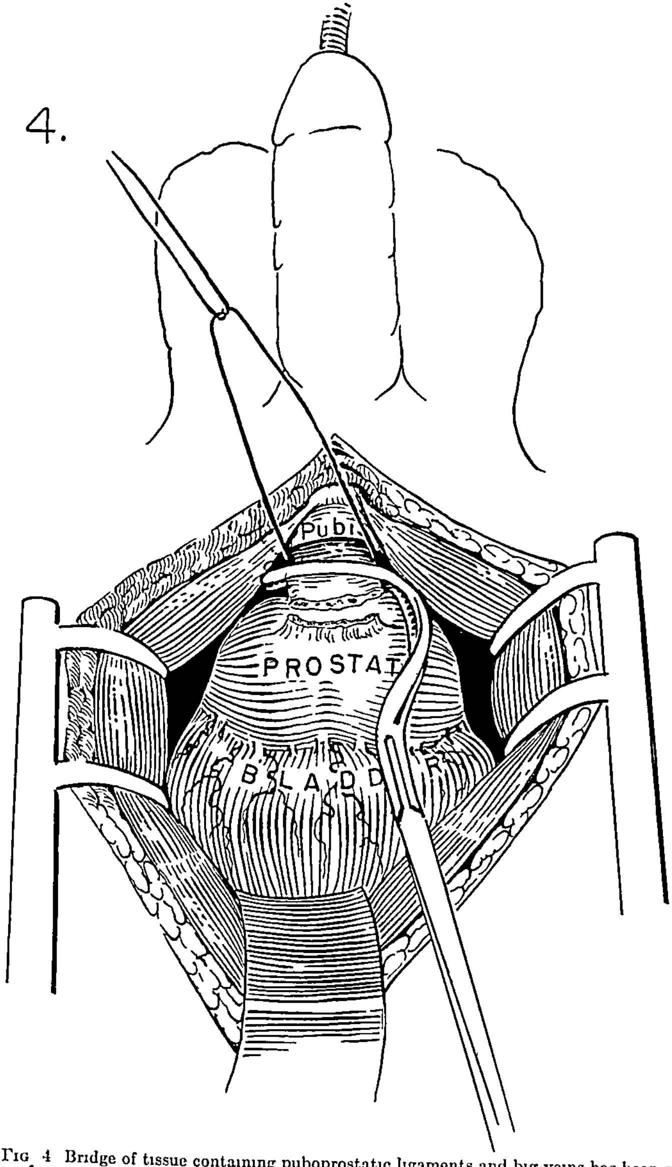

Fig 4 Bridge of tissue containing puboprostatic ligaments and big veins has been cut away from prostate and is being ligated

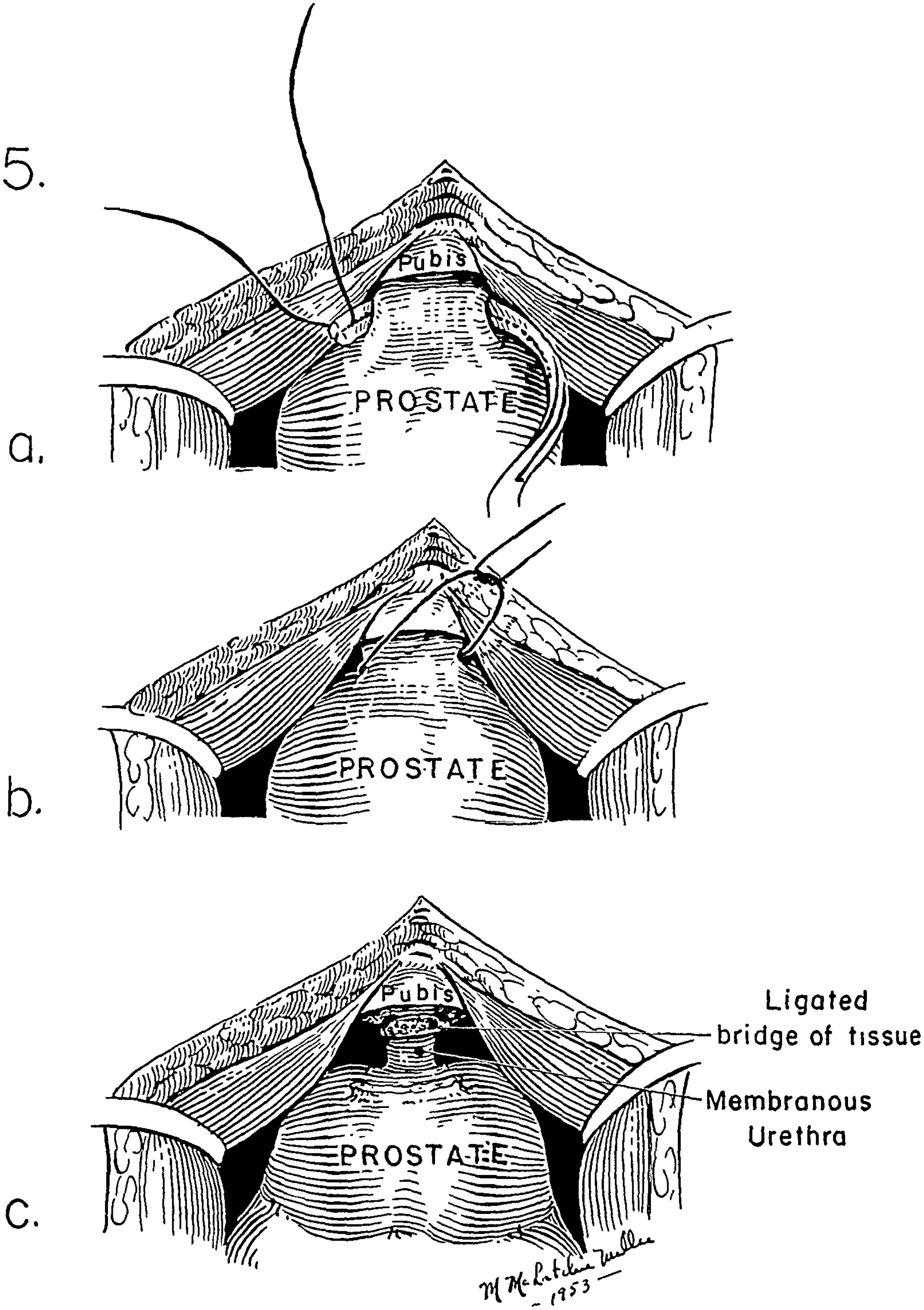

FIG. 5. Alternative and equally satisfactory method of ligating bridge of puboprostatic ligaments and large veins. *A*, gooseneck clamp draws a stout ligature under bridge of tissue. *B*, ligature being tied. *C*, ligature tied; upper end of bridge of tissue has been sectioned revealing membranous urethra immediately beneath.

First of all, what are the results in regard to cure of cancer? The operation has been being performed for such a short time that there are comparatively few cases where 5 years have elapsed since operation Two contributors each had one 5-year cure, and two others had a number of 3-4-year cures In general the results appear to equal those obtained by total prostatectomy by the perineal route Local recurrence seems to be rare, most of those who die of the disease succumb to distant metastases

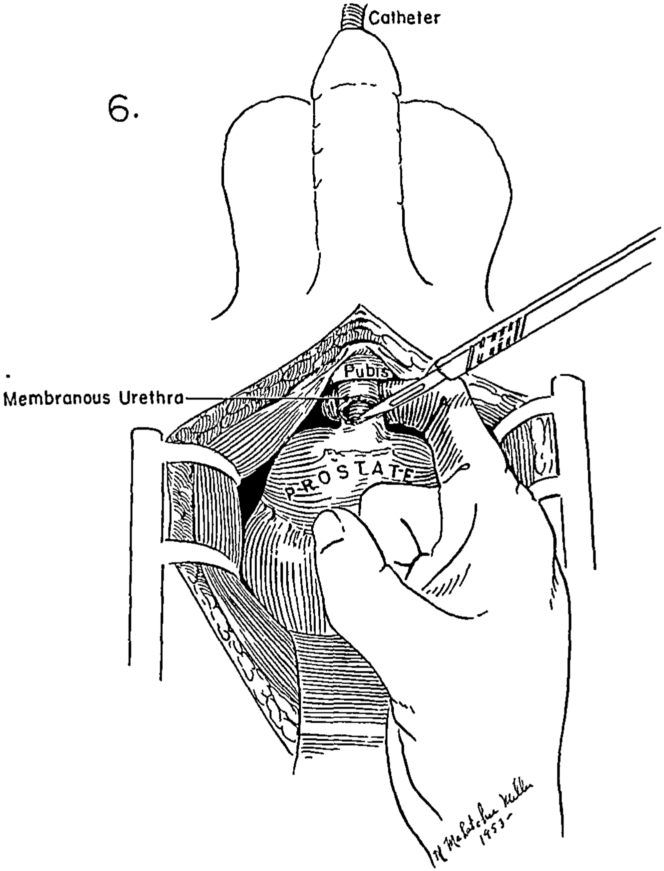

Fig 6 With finger beneath it, membranous urethra has been gently separated from underlying rectum, and its roof is being incised upon inlying catheter

What is the operative or postoperative hospital mortality? This is apparently what one would expect for prostatectomy in any good clinic, and averaged out at 2.7 per cent, which is certainly not excessive.

The next important question concerns the results in regard to postoperative urinary control. The truthful answer to this is that the results are approximately the same as in radical perineal prostatectomy. In other words, about two thirds of the patients have had satisfactory control within a short time after operation. However about 30 per cent have had partial or stress incontinence lasting occasionally as long as a year, and the very rare case has had permanently poor control. In my own mind, I expect that some degree of temporary partial or stress incontinence is a necessary evil not infrequently accompanying any total removal of the prostate for cancer, but it is a small price to pay for a good chance of having been cured of a fatal disease. When one thinks of permanent colostomies—and especially of the so-called "wet" colostomies draining both feces and urine—which many patients, men and women, gladly accept in return for an opportunity to live, temporary partial incontinence does not seem so bad.

The next question is, "What are the results in regard to the occurrence of rectal fistulas?" When one is working next to the rectum and separating structures from it, of course the possibility of traumatizing it always exists. However, in this operation there is less danger of injuring the rectum than there is in the radical perineal, as the exposure is much better, especially at the tips of the seminal vesicles, and the dissection is done under full vision and in a wound that is not so cramped. In the entire series there were only two injuries to the rectum. One of these was recognized immediately and repaired successfully. Another was recognized and repaired, but the patient died five days later of a cerebrovascular accident. One of the contributors saw a rectal fistula in a patient who had been operated upon by someone else.

What other complications have occurred in relation to these operations? In the early cases operative hemorrhage was somewhat of a challenge. However now that the technique of isolating and ligating the puboprostatic ligaments and their accompanying large veins has been evolved, hemorrhage is no problem. Also the final sutures holding the bladder outlet in position control any residual bleeding in this region. These matters will be described under the technique of the operation. As might be expected, some postoperative ooze in the pelvis occurs. Partly because of this, and partly to take care of any contaminating urinary drainage, a piece of empty soft rubber Penrose drain is always left in the pelvis on each side of the bladder base. Thus channelled to the surface, postoperative ooze or infection poses no problem.

Postoperative stricture at the new junction of the bladder outlet and urethra occurred in perhaps 15 per cent of cases, mostly in the early cases. The best prophylaxis against this is close approximation of the new bladder outlet to the membranous urethra at the time of operation, so that there will be no gap to be filled in by scar tissue—about which more later. Just as following radical perineal prostatectomy, in every case the possibility of the occurrence of stricture should be borne in mind, and sounds should be passed before the patient leaves the hospital, and also several times in the first few months following operation. Usually this will thwart any tendency to stricture formation. Three cases were reported where the new anastomosis healed with the formation of an obstructive band at the new bladder outlet—analagous to a fibrous median prostatic bar. This situation was easily rectified by transurethral resection of this band.

What of osteitis pubis, which is apparently more common in retropubic prostatectomies? In my questionnaire I forgot to ask about this. However, two contributors told me personally that they had had none. Millin feels that a possible reason why osteitis pubis occurs less commonly in radical prostatectomies is because the floor of the retropubic space is removed and thus the area behind the pubis is well drained. One contributor had osteitis in a case in which he had made a transverse abdominal incision, sectioning the tendons of the rectus muscle close to the pubic symphysis according to the Cherney technique. Whether that may have been an etiological factor or not, he does not know, but he has not sectioned the tendons in that manner since, and has had no further cases of osteitis.

The operation of radical perineal prostatectomy has one advantage over the retropubic operation, and that is the ability to perform biopsy as a preliminary part of the operation. In many cases one is sure of the diagnosis of carcinoma by rectal palpation, or by transurethral biopsy, or by biopsy through the perineum by one of the various biopsy needles (Silverman, Cahill, or Turkel). However there are a few cases where there is no obstruction to urination to justify prostatectomy regardless of malignancy and where the suspicious area is small or buried in the gland, in which biopsy of the posterior portion of the exposed prostate via a perineal incision appears to be the best procedure. In such cases, the result of the immediate microscopic examination of this frozen tissue removed at biopsy will determine whether an immediate radical prostatectomy through the same open perineal incision is to be done, or a conservative prostatectomy, or even no prostatectomy. Preliminary direct surgical biopsy of the posterior portion of the prostate is not feasible by the retropubic route because, by the time the posterior portion of the prostate is exposed, the puboprostatic ligaments and membranous urethra have been severed, and the operation is nearly half over.

A second advantage of the perineal over the retropubic procedure is that the perineal approach seems to carry somewhat less shock. However, radical retropubic prostatectomy is not a shocking operation, and I do not believe that the lesser shock of the perineal is of very great practical importance, except occasionally in very frail, poor risk patients.

In my opinion, these two matters of preliminary biopsy as part of the operation and of somewhat less operative shock are the only advantages of the perineal over the retropubic operation.

Let me now describe the simple technique which I have used and found quite satisfactory.

The urinary tract is prepared with a urinary antiseptic, such as gantrisin, one to two grams four times per day. Either spinal or ether anesthesia is used. A sand bag is placed under the patient's hips in order to hyperextend him slightly, or the same effect is obtained by breaking the operating table a little. If the patient has been on constant drainage with a catheter, that catheter is now removed. The perineum is prepared and draped as well as the abdomen. Now a sterile, large (No. 24 or 26) Foley catheter with a 30 cc bag is placed in the bladder, and the bag inflated with water. The end of the catheter is left open and draining onto a sterile towel between the patient's legs. Either a transverse or vertical suprapubic incision is made, and a self-retaining retractor of the Balfour

7.

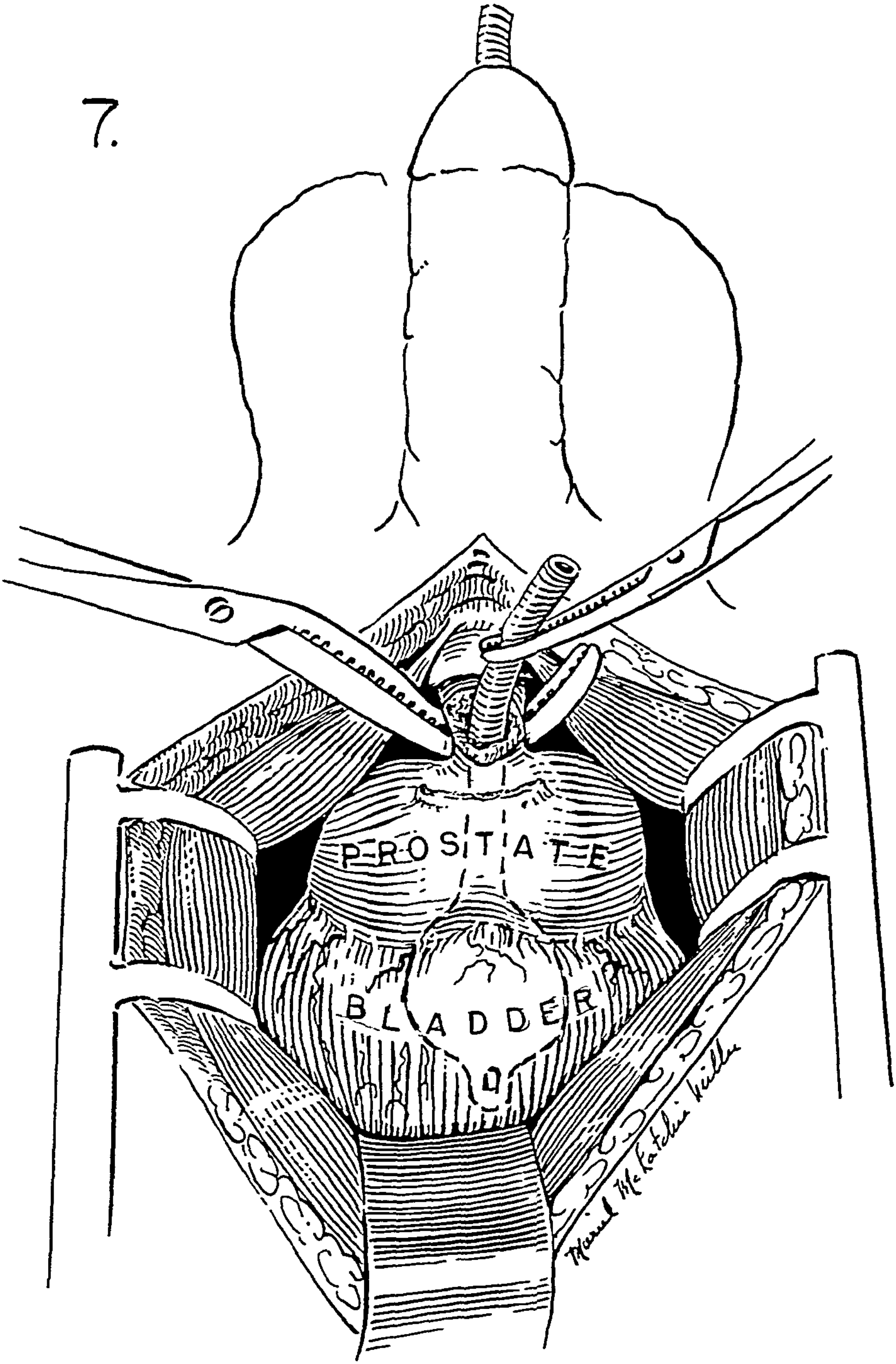

FIG. 7. Through incision in roof of membranous urethra, catheter is picked up and clamped, and distal end cut off and discarded. (In order to demonstrate floor of membranous urethra, curved clamp is shown beneath it.)

or Millin type is inserted, but no retraction is made against the pubic symphysis The prevesical fat is pushed aside to expose the prostate Any veins which it is necessary to disturb are clamped, sectioned, and coagulated with the electrosurgical current (fig 1) Now that the prostate is exposed, the finger is thrust down through the endopelvic fascia on either side of the prostate into the pelvis and into an excellent cleavage plane This maneuver is very important (fig 2)

8.

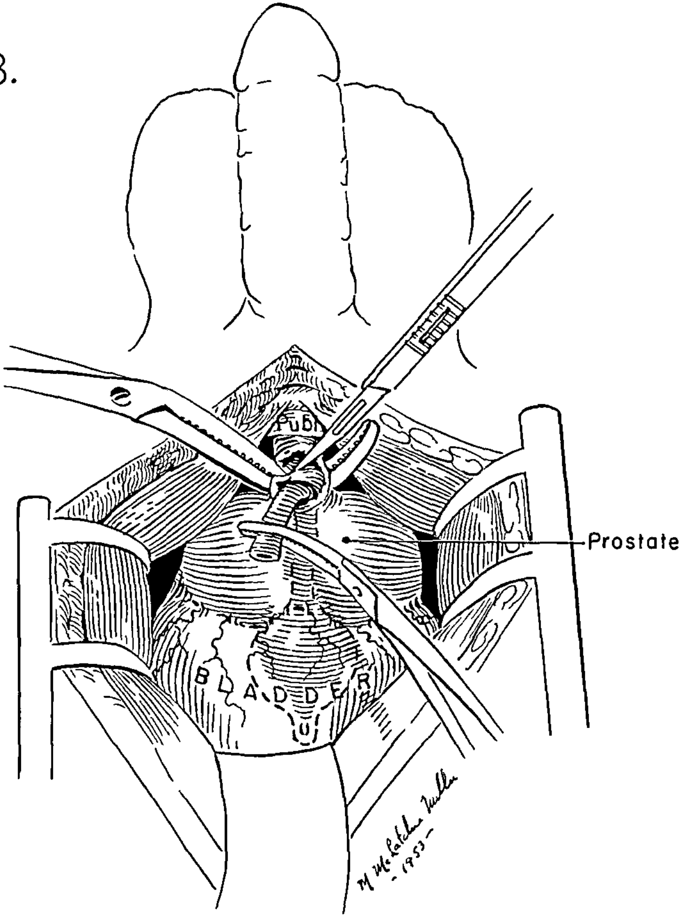

Fig 8 Foley catheter is retracted upward and floor of membranous urethra is sectioned

The finger on each side of the prostate is now worked forward and towards the midline where the urethra is. The finger keeps the urethra (easily identified by the large catheter in it) below, and separates it from the bridge of tissue containing the puboprostatic ligaments and very large veins which is kept above the finger. Then this bridge of tissue above is ligated with a stout piece of chromic No. 1, and sectioned on the prostatic (upper) side of the ligature (figs. 3–5). This prevents bleeding from the plexus of Santorini. If for any reason, such as the

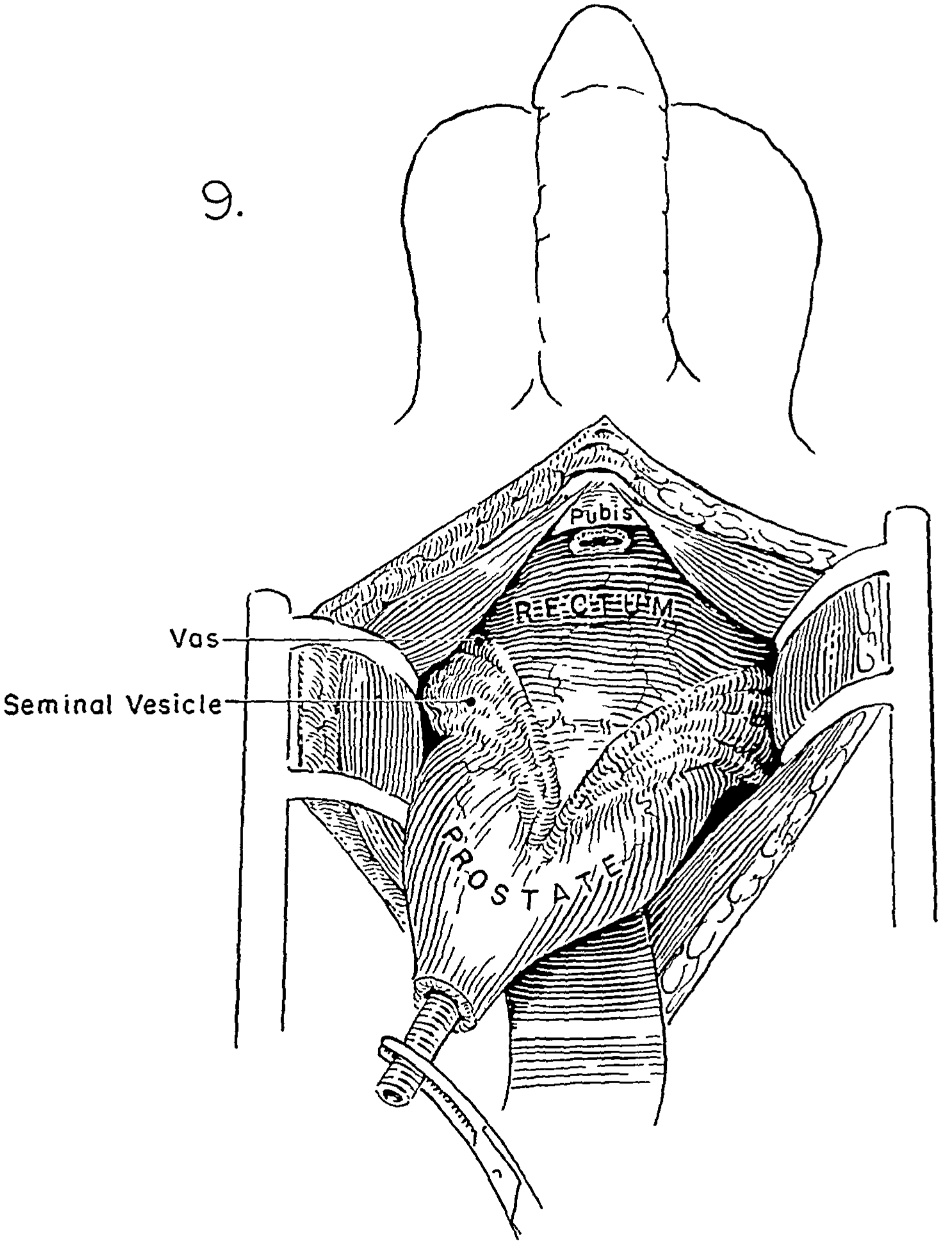

FIG. 9. Using Foley catheter for traction, prostate, seminal vesicles and vasa are pulled upward and easily separated from rectum.

ligature slipping, profuse bleeding comes from this plexus, it can always be controlled by a gauze pack held in place under moderate pressure by a retractor for 15 minutes or so, meanwhile carrying out some other step of the operation. After cutting this bridge of puboprostatic ligaments and veins, the membranous urethra

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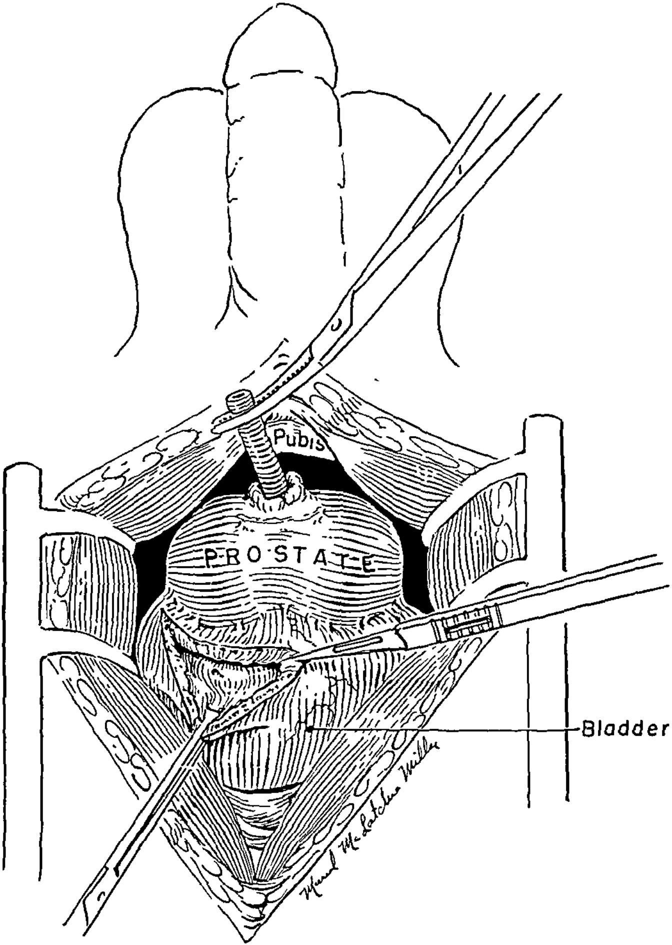

FIG. 10. Prostate is pulled down, and anterior wall of bladder is incised horizontally somewhat above prostate.

The finger on each side of the prostate is now worked forward and towards the midline where the urethra is. The finger keeps the urethra (easily identified by the large catheter in it) below, and separates it from the bridge of tissue containing the puboprostatic ligaments and very large veins which is kept above the finger. Then this bridge of tissue above is ligated with a stout piece of chromic No. 1, and sectioned on the prostatic (upper) side of the ligature (figs. 3–5). This prevents bleeding from the plexus of Santorini. If for any reason, such as the

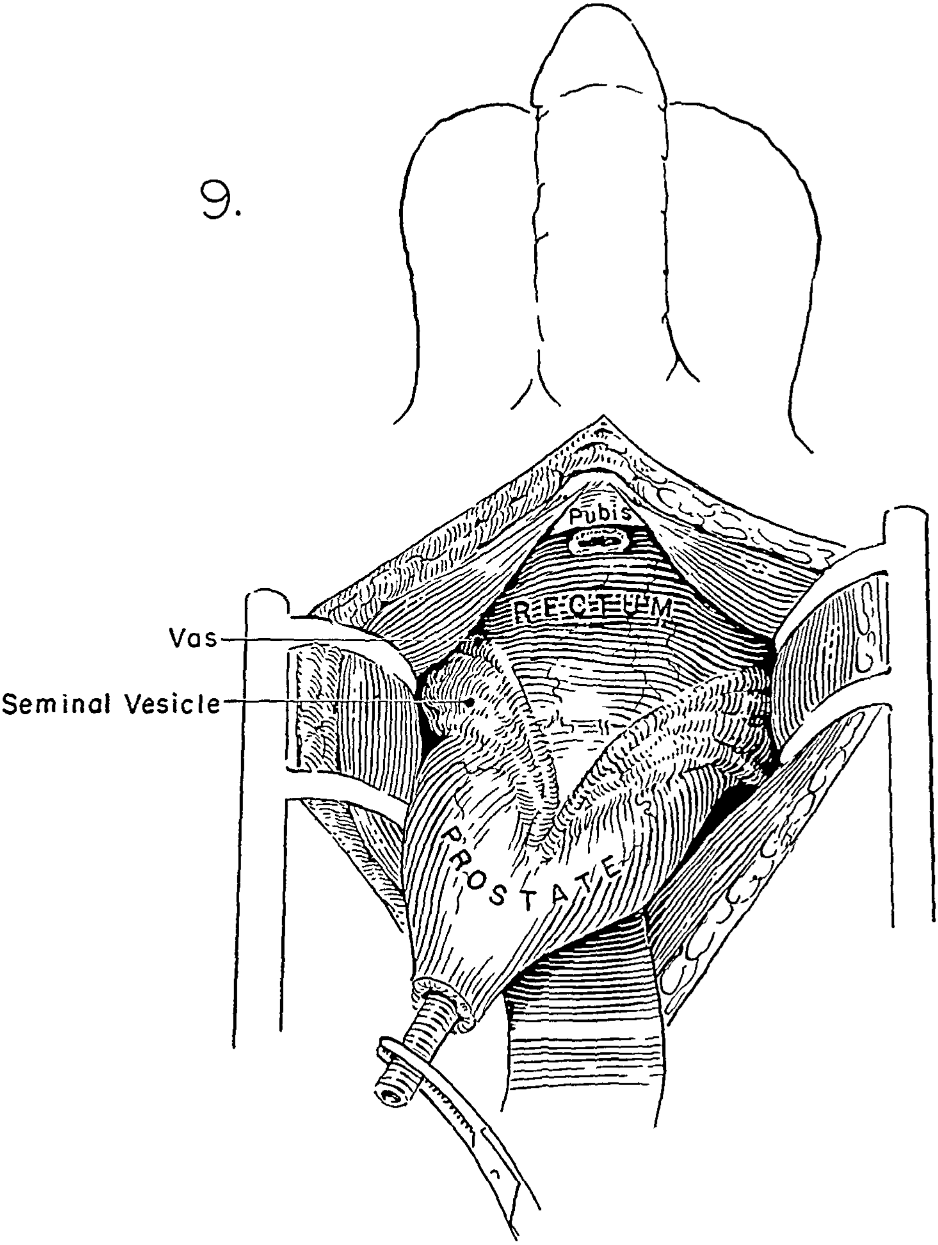

FIG. 9. Using Foley catheter for traction, prostate, seminal vesicles and vasa are pulled upward and easily separated from rectum.

containing the catheter comes into view beneath it Very gently the finger is insinuated under the membranous urethra, and separates it and the apex of the prostate from the rectum beneath Then the roof of the membranous urethra (rather near the prostate) is incised transversely, and the catheter is lifted up out of the urethra (fig 6) The catheter is then clamped (in order to keep the fluid in the bag), transected on the side of the clamp away from the prostate, and then is used to draw the prostate upward (fig 7) At this point the remaining part (floor) of the urethra is transected (fig 8) By traction on the clamp on the catheter the

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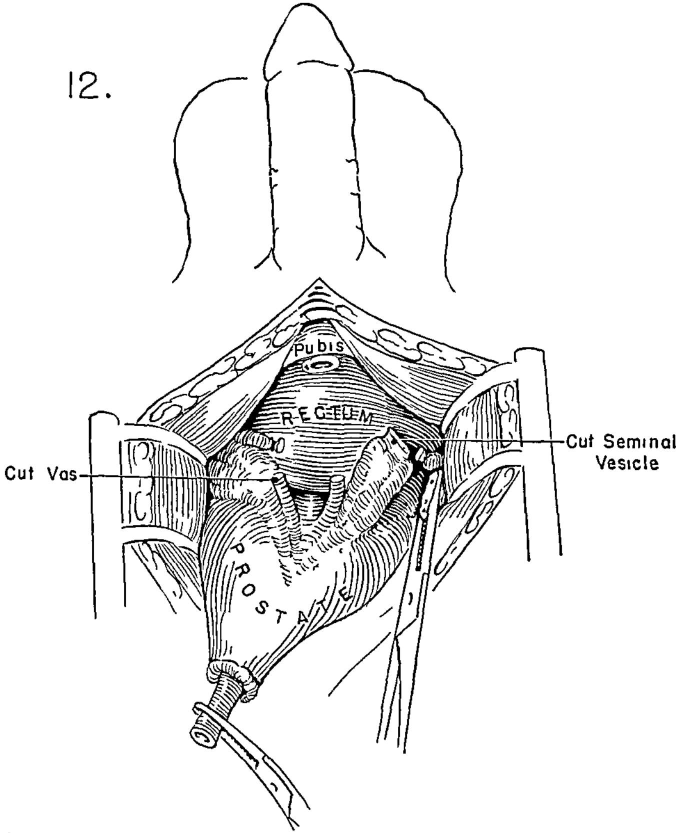

FIG 12 Both vasa have been sectioned and ligated Right seminal vesicle has been dissected free, and its pedicle clamped Left seminal vesicle has not yet been dissected free

prostate is elevated upward, and gently separated from the rectum beneath as far back as the vesicles (fig. 9). This is probably the most delicate part of the operation. At this point, an ampule of indigo carmine is given intravenously by the anesthetist. Now the prostate is pulled down again and a horizontal opening

13.

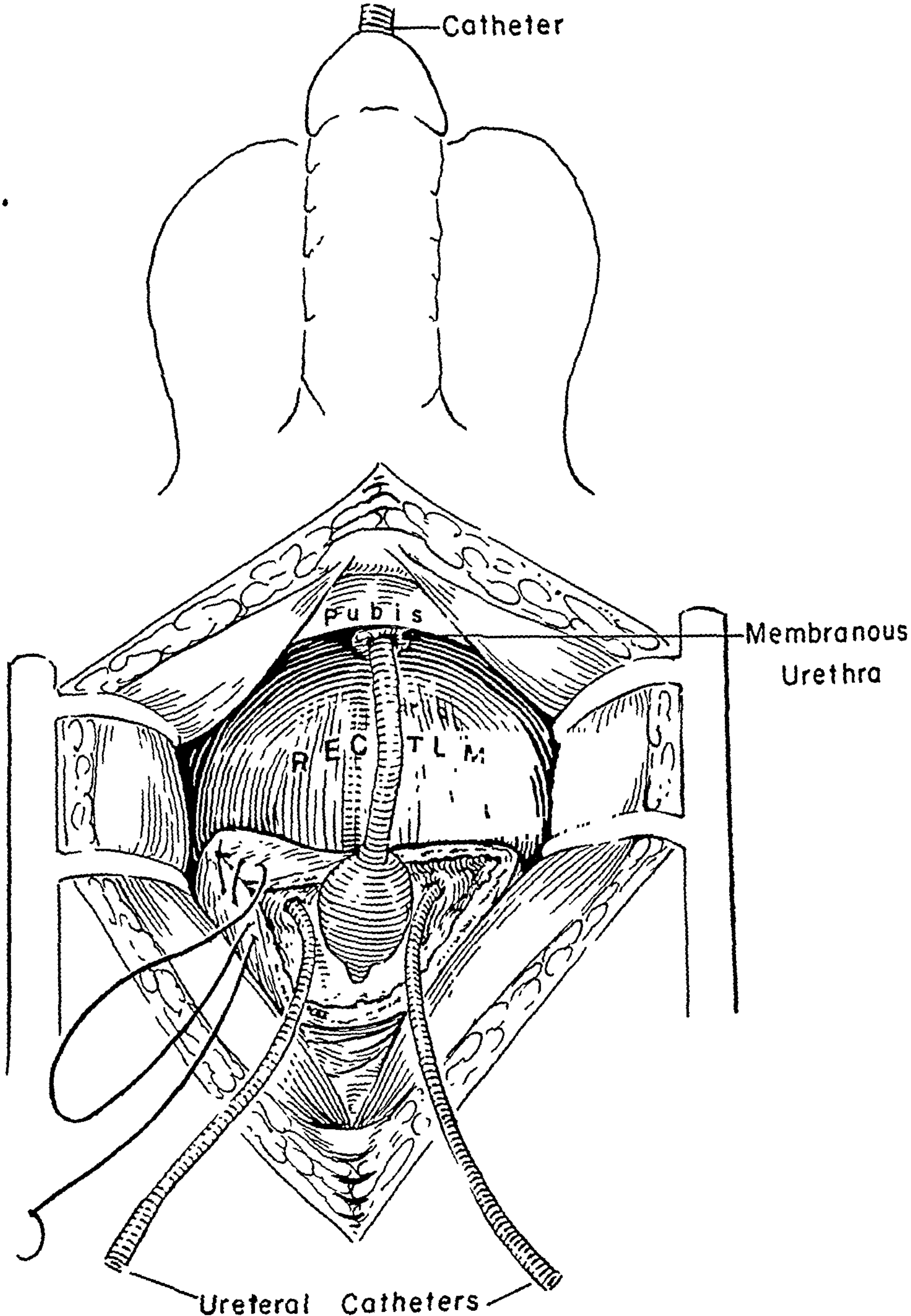

FIG. 13. Bladder is being closed in form of inverted Y about Foley catheter which will be brought out at upper end of stem of Y.

made with a knife through the anterior wall of the bladder a little above the prostatic margin (fig. 10). This opening is enlarged with scissors in a lateral direction on each side for an inch or so, but no further in order to avoid damaging the ureteral orifices. A retractor is inserted in the bladder, the ureteral orifices, now spurting blue indigo carmine, are located, and a No. 6 ureteral catheter is put up each one and left in place. Now, with the orifices well marked, the incision in the bladder is carried down each side and then across the trigone a little below the orifices (fig. 11). The trigone is dissected free from the underlying vesicles before sectioning it. This dissection is greatly helped by passing right-angle forceps under the trigone, opening and closing the jaws and advancing them, and then

14.

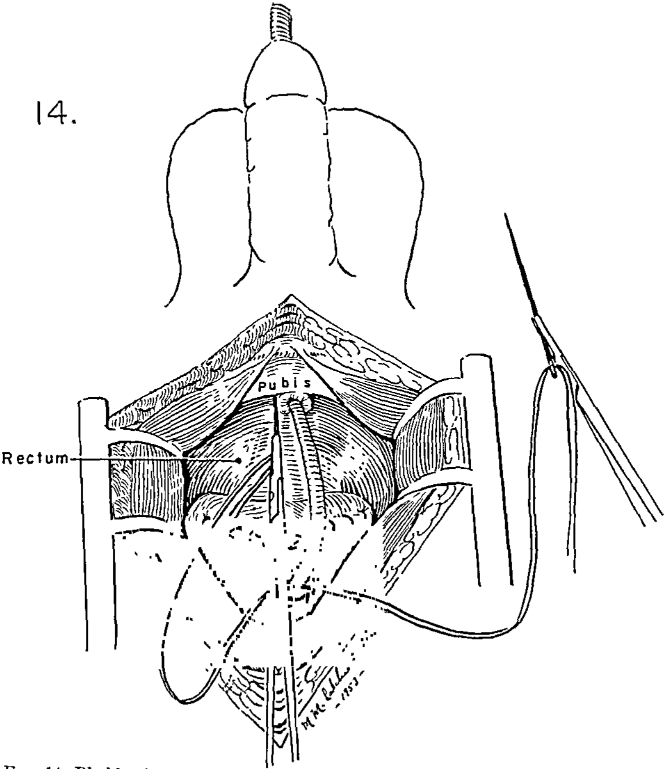

FIG. 14. Bladder has been closed in form of inverted Y about Foley catheter. Long doubled suture has been placed in bladder on each side of Foley catheter. By means of straight needles, these will be inserted on each side of membranous urethra and brought out on skin of perineum.

15.

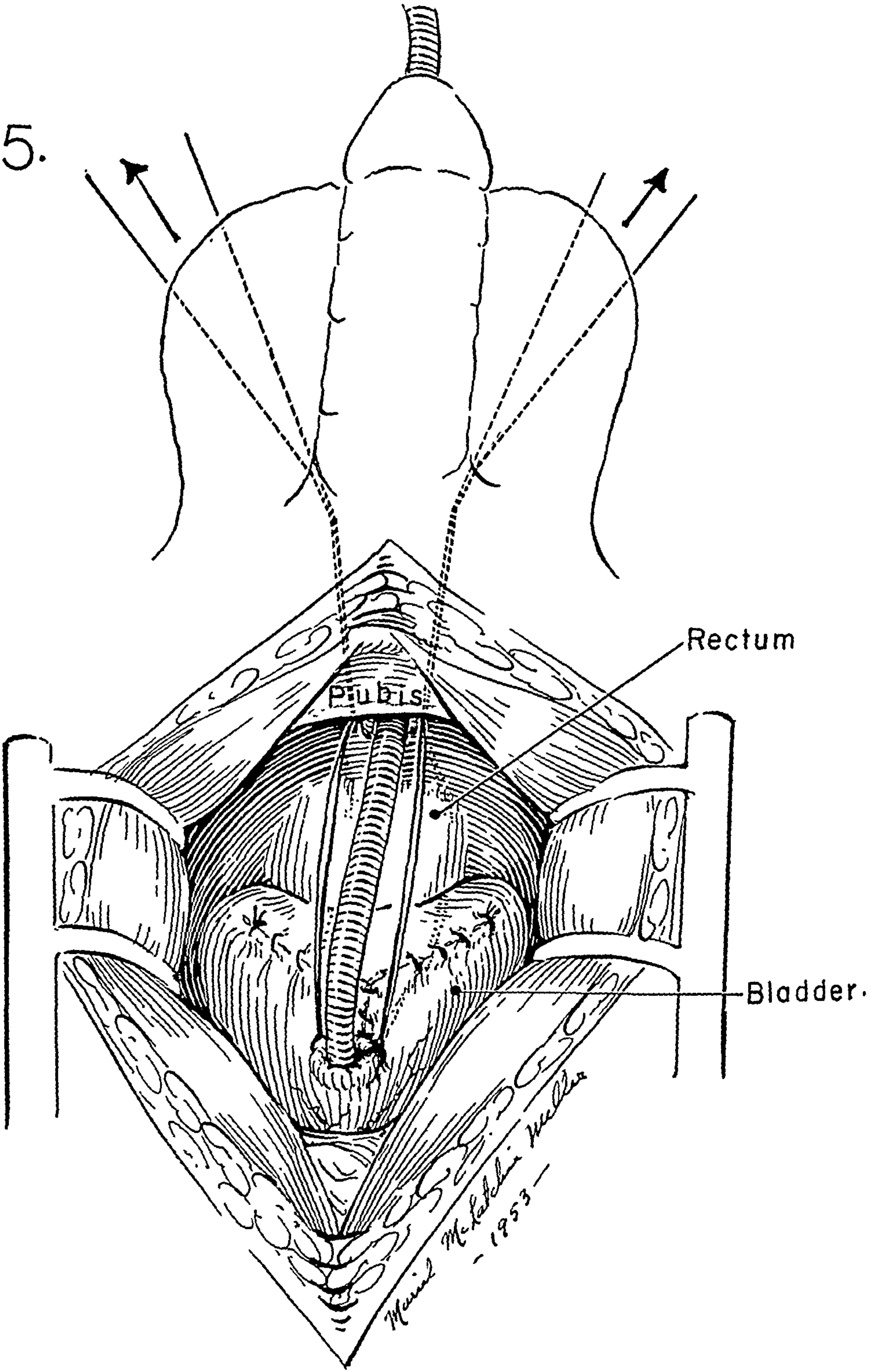

FIG. 15. Two long traction sutures on either side of catheter have been brought through perineum. Traction on them will pull future bladder neck snugly against membranous urethra.

cutting down between the jaws Then the vasa, which lie in the middle between the seminal vesicles, are ligated and sectioned individually Now the prostate is again retracted upward and each seminal vesicle, accompanied by a considerable amount of perivesicular tissue, is dissected free from the rectum, followed down beyond its tip, cut, clamped, and ligated Suture ligatures of chromic 0 are best used in this somewhat deep hole (fig 12) When this has been done on each side, the prostate is free During this last dissection it is very helpful and reassuring to have the ureteral catheters in place to show the location of the ureters and thus to guard against damaging them while dissecting back up under the bladder If the ureter is cut accidentally or its lowest end is compromised by tumor extension and has to be sacrificed in order to remove the disease, it can easily be reimplanted higher up in the bladder Now the wide open end of the bladder is closed around

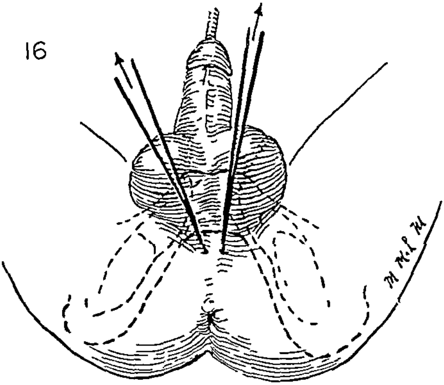

FIG 16 This shows two long traction sutures on bladder emerging from perineum

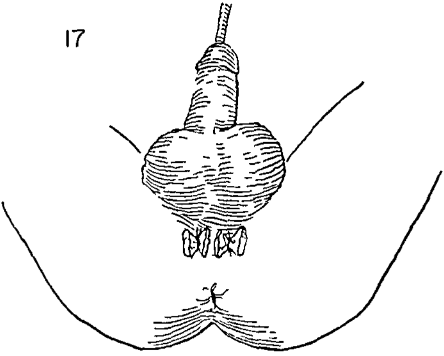

FIG 17 Two long traction sutures on bladder have been tied over rolls of gauze on perineum, thus pulling new bladder outlet down to membranous urethra

18.

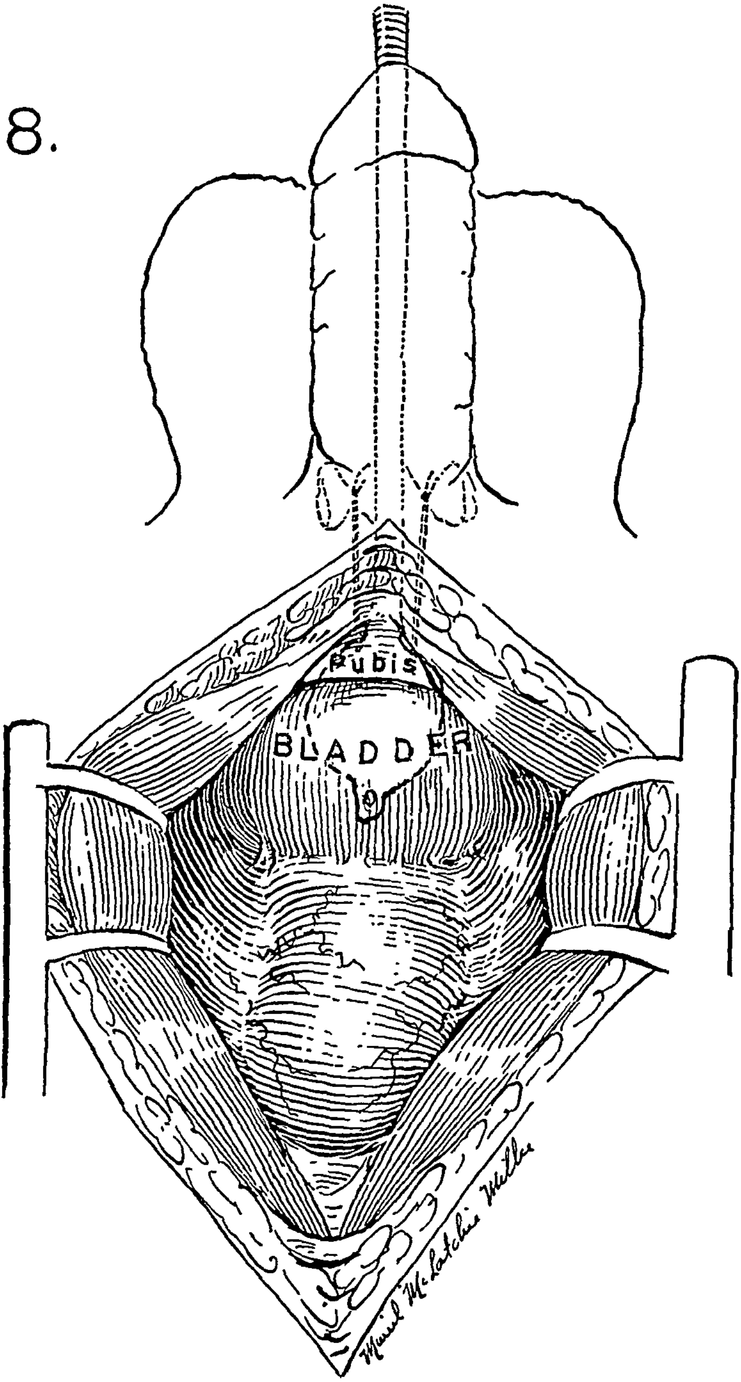

FIG. 18. Showing how future bladder neck is pulled down and held approximated to membranous urethra when two long traction sutures are tied over small rolls of gauze on perineum. Snug approximation is further ensured by pulling Foley bag down on bladder outlet by maintaining some tension on catheter.

a new No 20 Foley catheter with a 30 cc bag inflated to 15 cc which has been introduced through the urethra (fig 13) It is best to close the bladder vertically in the form of an inverted Y, and bring the catheter out high up anteriorly near the upper end of the vertical wound This part of the bladder is much more mobile than the trigone and can be pulled down to the membranous urethra without tension, which it is extremely important to avoid Also it is of very great importance to be sure to avoid catching or constricting the ureteral orifices with sutures, and for this reason the ureteral catheters are left in place until after the suturing of the bladder in their vicinity is completed In the vertical closure with the inverted Y, the purpose of the limbs of the Y is to keep the trigone and ureteral orifices from being pulled together and compressed too much as would happen in an absolutely vertical wound Anastomosing the new bladder outlet to the membranous urethra with a series of stitches is very difficult and time-consuming, and I use a technique showed me by Dr Lytle Atherton of Louisville, Kentucky which has given both him and me good results It is an adaptation of the Vest traction sutures often used in perineal prostatectomy, and is

19.

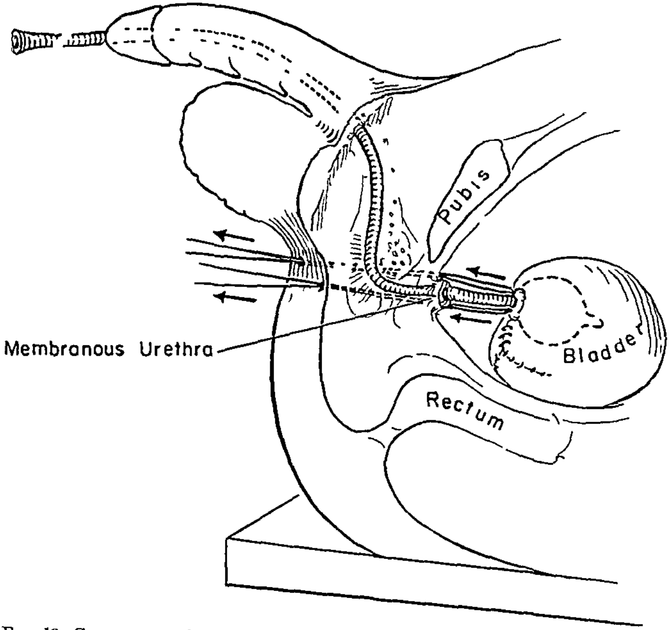

FIG 19 Cross section showing traction sutures on bladder neck emerging on perineum, but not yet tied

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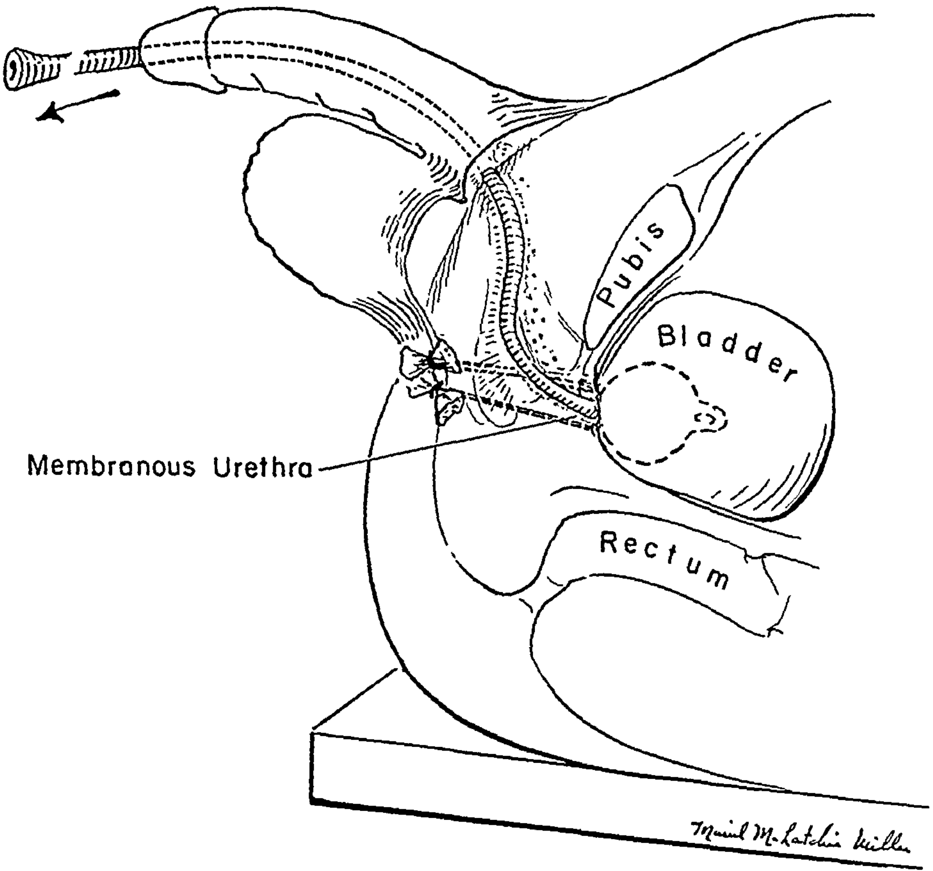

FIG. 20. Cross section showing how bladder outlet is held closely approximated to membranous urethra after traction sutures have been tied on perineum and traction put on Foley catheter.

performed as follows: After the bladder has been closed about the catheter, another suture of No. 1 chromic is placed just lateral to the outlet and the catheter, and both ends are left eight inches long. A similar suture is placed on the other side of the bladder outlet. Both strands of the suture on the right are now threaded on a long straight needle (figs. 14–20) and this needle is inserted just to the right of the membranous urethra and passed straight through and out on to the skin of the perineum just to the right of the midline not far behind the scrotum. The left suture is passed out on the left side in a similar manner. By pulling on these sutures the new bladder outlet is brought snugly down to the membranous urethra, the catheter acting as a guide and splint. The two ends of the right suture are tied together over a small roll of gauze on the perineum, and a similar procedure is carried out with the left suture. These sutures are left in place for twelve days, but sometimes come away spontaneously earlier. An empty Penrose rubber drain is put down into the depth of the pelvis on either side of the bladder to take care of postoperative oozing and any urinary drainage, and these drains are brought out through the wound. They are not touched until the

21.

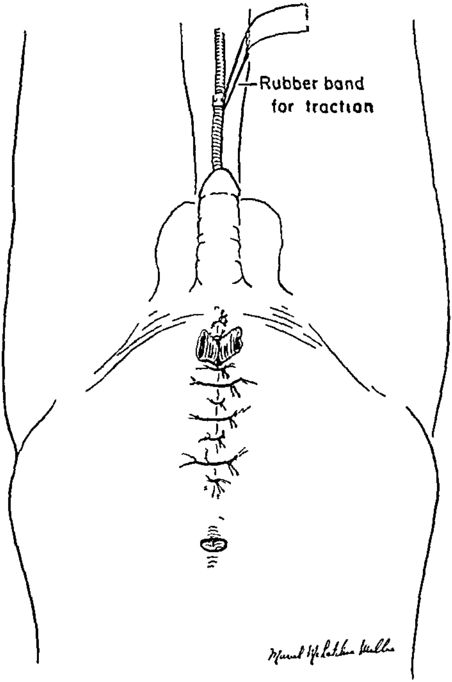

FIG 21 Abdominal wound has been closed Stay sutures are used Two empty rubber wicks in pelvis on either side of bladder outlet are brought out through lower end of wound Some traction is maintained on Foley bag catheter by means of rubber band attached to thigh by adhesive tape

patient's temperature has been normal for twenty four hours They are "started" and gradually removed over the course of several days The wound is closed as usual with interrupted catgut sutures and through and through stay sutures (fig 21) As a final maneuver the Foley catheter is pulled down snugly on the bladder outlet and *put on slight tension with a rubber band to the thigh* The catheter is left in place twelve to fourteen days If there is any oozing which persists from the big veins of the pubo prostatic region (plexus of Santorini), this always stops after the bladder outlet has been pulled down snugly against this region by the traction sutures and the tension on the Foley bag

SUMMARY

Carcinoma of the prostate is surprisingly common, the average of the figures of four independent investigators giving an incidence of 24 per cent in a large series of routine autopsies in men 50 years of age or over Most of these carcinomas were small, and had not spread beyond the gland or been the cause of death—and also had not been diagnosed clinically. It is estimated that there are from 2,333,000 to 7,500,000 men over fifty in the U.S. with carcinoma of the prostate, and that in from 195,000 to 1,500,000 of these the disease is in a stage early enough to be probably curable by surgery.

The investigations of the foregoing, and of other men indicate that carcinoma of the prostate is usually a slow-growing tumor, and that it goes through a stage when it is still confined inside its capsule, where it can readily be detected by rectal palpation, before it escapes from the capsule and spreads and metastasizes.

That such a type of tumor is amenable to cure by radical surgery, if detected in time, is evidenced by 5-year cure rates averaging 50 per cent following radical perineal prostatectomy in the hands of several experts in this operation. These results are definitely superior to the 43 per cent of 5-year survivals, but with disease still present, reported in a very large number of cases treated by orchiectomy and/or estrogenic therapy.

Despite the favorable results of radical surgery in cases detected in the early stage, the cure rate of cancer of the prostate throughout the country is low. This is due to two reasons:

1) In the majority of cases, the disease progresses so silently that by the time it causes symptoms bothersome enough to lead the patient to consult a physician, it has already spread and become inoperable locally, and possibly has also metastasized. The only defense against this is an educational program for an annual physical check-up, including rectal examination, of all men over fifty.

2) Although radical perineal prostatectomy, in early cases, has produced the previously quoted results definitely superior to those of hormonal therapy, which is palliative only, nevertheless most urologists will not perform this operation. This is assumed to be because the majority of urologists have not been trained to do the radical operation and, realizing that an error in technique may result in incontinence or a recto-urethral fistula, therefore prefer riskless hormonal therapy—with transurethral resection as necessary—which usually will give a few years of satisfactory palliation.

As an antidote for this bad situation another operation recently has been developed for the total extirpation of the cancerous prostate, radical retropubic prostatectomy, which the author believes is destined to gain great flavor with urologists. This operation gives results just as good as the radical perineal as regards the cure of cancer, carries no greater mortality, is easier to perform, and there is less danger of rectal fistulas. Postoperative incontinence is about the same as following the radical perineal by the best operators. Osteitis pubis is rare. Abdominal exploration or dissection of pelvic nodes, both impossible via the perineal approach, can be carried out. The injection of radio-active gold, if extra-prostatic spread is found, can be done in conjunction with it.

The results of the author's small series of cases together with results generously contributed by Mr. Millin and Doctors Mammelaar, Flocks, and Atherton—the whole series representing more than 200 cases—are discussed.

The author's technique of radical retropubic prostatectomy is described in detail with drawings.

203 Commonwealth Ave., Boston 16, Mass.

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CRYPTOCOCCOSIS (TORULOSIS) INVOLVING THE BRAIN, ADRENAL AND PROSTATE

HAROLD E BOWMAN AND JAMES O RITCHEY

From the Departments of Pathology and Medicine, Indiana University School of Medicine, Indianapolis, Ind

Cryptococcosis is a subacute or chronic infection and the lesion may occur in any part of the body The fungus involves primarily deep seated organs with a predilection for the brain The causal agent is a Cryptococcus (frequently called Torula histolytica), a yeast like fungus reported from many parts of the world Some confusion exists in nomenclature, but the terms "cryptococcosis" and "torulosis" are used interchangeably to designate the disease caused by this type of fungus Most of the cases have been reported from the United States The entity is thought to be ordinarily fatal Since 1933, five cases of systemic infection due to cryptococcus have been seen at the Indiana University Medical Center Four of these cases were proven by autopsy examination and bacteriologic cultures

At present approximately 223 cases have been recorded since 1916 Perhaps, torulosis should no longer be considered an obscure or extremely rare disease In light of the protean clinical manifestations of this infection, several diseases are generally considered before the diagnostician thinks of a systemic fungus infection

This paper reports a new case and mentions briefly three other cases seen at the Indiana University Medical Center

CLINICAL HISTORY

A 52 year old white man was admitted to the Robert Long Hospital, Indiana University Medical Center on November 20, 1950 His chief complaints were lethargy, unexplained fever of four to six weeks' duration, and mild diabetes Previous penicillin therapy had failed to bring his fever under control At the time of admission the patient's physical examination was negative except for a moderate horizontal nystagmus, a questionable papilledema of the left eye, and absent abdominal and cremasteric reflexes The patient was confused and disoriented when admitted The patient's mental attitude remained unchanged throughout his course in the hospital Multiple lumbar punctures demonstrated a slight increase in spinal fluid pressure, an increased number of cells (lymphocytes predominated), a decreased amount of spinal fluid sugar and an increased amount of protein with a positive Pandy test An extensive study of the spinal fluid and urine failed to reveal acid fast bacilli or other bacteria on smear or culture Ventriculography was performed on December 7, 1950 and there was a marked dilatation of the lateral ventricles of the brain

The patient's course in the hospital remained uneventful His diabetes was controlled by diet The temperature occasionally rose to 102F and the patient

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was incontinent of urine and feces. A second strength Mantoux test was negative. The patient was released from the hospital on December 18, 1950 and succumbed at his home on December 28, 1950. The body was returned to Robert Long Hospital for post-mortem examination. The discharge diagnosis was probable tuberculous meningitis, although torulosis had been considered during clinical study.

Significant laboratory studies during the hospital admission: Urinalysis uninformative; Mazzini negative. Hemogram: hemoglobin 12.0 grams, red count 4,010,000, white count 8,550, differential, moderate shift to the left. On repeated spinal fluid examinations, the white count varied between 50 and 200 cells. A representative differential: polys 12, lymphocytes 88, the Pandy varied from 4+ to 3+. A trace of xanthocromia was noted in most specimens. The sugar was consistently below 14 mg. per cent. The total protein varied between 576 mg. per cent and 320 mg. per cent. Blood cultures and spinal fluid cultures were negative. Urine culture yielded an organism which was later identified as Cryptococcus neoformans.

Sections of dura and tissue obtained at ventriculography showed dura mater with small areas of calcium deposition. The cerebrum demonstrated non-specific toxic or degenerative changes. By means of ventriculography, there was demonstrated a symmetrical hydrocephalus throughout the ventricular system with no evidence of a space occupying lesion. Roentgenograms of the chest taken one week before death were negative. On two occasions films of the skull showed the pineal calcification in a normal position on both the anterior, posterior and lateral projections. The sella turcica was normal and no cranial or intracranial abnormalities were found.

POSTMORTEM FINDINGS

The patient was 52 years of age, approximately 6 feet tall and weighed 160 pounds. Bitemporal and parietal burr holes of the skull were present and well healed. The only gross finding of significance in the abdomen was a mass of bright yellow tissue (measuring 12 by 15 mm.) in the left adrenal gland. The left pleural cavity was obliterated by dense fibrous adhesions. The left lung was grossly normal. In the right lung there was consolidation of the lower lobe and inferior portion of the middle and upper lobe. A few mediastinal lymph nodes were caseous, bluish-black and of normal size. Over the brain and meninges in patchy areas, there was a thin yellow-green exudate of creamy to gelatinous consistency. Similar exudate covered the ependyma and choroid plexus, and filled the greatly dilated third and fourth ventricles. There was an obstruction at the floor and posterior end of the fourth ventricle by the gelatinous fluid.

Microscopic examination of the sections removed at autopsy demonstrated a granulomatous type of reaction in the brain and meningeal tissue. There were present many epithelioid cells lying in a delicate reticulum infiltrated by large mononuclear phagocytes and lymphocytes. Many foreign body giant cells were present. In some areas there was a close network of connective tissue reticulum, with fibroblasts and epithelioid cells in whorls and an occasional

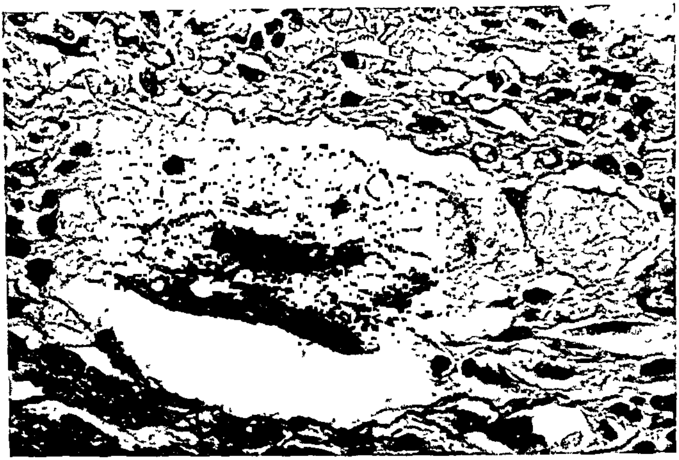

FIG. 1. Microphotograph from involved meninges of brain. Two giant cells are present in field, each filled with the yeast-like organisms. Refractile capsule is prominent in several instances. Note infiltrating cells are predominately mononuclear. Similar phagocytosed organisms were seen in adrenal and prostate glands.

giant cell. In several areas in the meninges caseation necrosis was present. The inflammatory process extended along the cerebral vascular channels into the cortical substance and many small blood vessels in the brain and the meninges demonstrated perivascular infiltration of lymphocytes. In the cerebral cortex in a few foci a granulomatous lesion was noted. Throughout the granulomatous areas there were yeast-like organisms within giant and epithelioid cells (average number ten to twenty per cell). (See figure 1.) The organisms appeared as small basophilic spheres ranging from five to seven micra in diameter, in the free form demonstrating a refractile capsule. A few of the organisms were noted free among the cells of the exudate. The yeast cells rarely were found in the budding form. Along the base of the pituitary there was a small area of caseation necrosis containing the organisms.

In the sections taken through the tumor in the left adrenal, there was a granuloma similar to that seen in the meninges. The central portion of the mass displayed caseous necrosis and the yeast-like organisms were present.

In the prostate there was a granulomatous reaction similar to that seen in the adrenal and meninges containing Cryptococcus neoformans.

The right lung showed bronchopneumonia with dependent atelectasis and passive congestion. No signs of mycotic infection were demonstrated even though a large number of sections were prepared.

The final autopsy diagnosis was meningo-encephalitis due to Cryptococcus neoformans (Torula histolytica) with involvement of the left adrenal and prostate.

DISCUSSION

Freeman[1] mentions Zenker's report in 1861 of a fatal case of central nervous system involvement by a yeast-like fungus. The causative organism may have been Cryptococcus neoformans. In 1916 Stoddard and Cutler[2] in their monograph placed the pathologic and clinical picture of torulosis on a firm basis and attempted to differentiate the entity from other fungus infestations. They gave the organism the name Torula histolytica. Since that time case reports and reviews of the literature on torulosis have appeared with increasing frequency.[1, 3, 4, 5, 6]

Torulosis occurs in all parts of this country. There are no known instances of transmission from animal to man or from man to man. The disease may occur at any age, but it appears to be most prevalent between the ages of 40 and 60; males are reported infected twice as frequently as females. All races seem to be equally susceptible. In the most commonly recorded infection the brain and meninges are involved.

The clinical symptoms are generally those of a slowly developing meningitis. The onset is insidious, with headache, dizziness, vertigo and stiffness of the neck. Rarely are the classical signs of acute meningitis noticed. The patient has little or no fever; the pulse and blood pressure remain normal. The patient may present only multiple subcutaneous abscesses. The lungs are generally involved and the primary pulmonary lesion resembles primary carcinoma or re-infection tuberculosis on roentgenograms. It is presumed that the fungus enters the body through the respiratory tract and the first lesions are in the lung with extension to the central nervous system. However, there have been cases in the literature to support contention that the yeast organism invades the central nervous system directly through the upper respiratory tract.[7] Cohen and Kaufman[6] believe the primary focus may be from the prostate gland since in their case the organisms produced little tissue reaction in the prostatic acini as compared to the extensive tissue damage in the lungs and central nervous system. We found evidence of rather severe tissue changes in the prostate gland in our case accompanied by caseous necrosis—which would tend to refute the premise of Cohen and Kaufman[6] that because of the lack of tissue reaction in that site, the prostate was a possible primary focus. We believe the portal of entry is yet to be proved.

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[1] Freeman, W.: Torula infection of central nervous system. J. f. Psychol. u. Neurol. **43:** 236–345, 1931.

[2] Stoddard, J. L. and Cutler, E. C.: Torula infection in man. Studies from Rockefeller Institute for Medical Research Reprints, **25:** 1, 1916.

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[5] Mosberg, W. H. and Arnold, J. G.: Torulosis of central nervous system: Review of literature and report of 5 cases. Ann. Int. Med., **32:** 1153–1183, 1950.

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The diagnosis of Torula meningitis cannot be made on the basis of clinical signs and symptoms alone The entity may be confused with syphilitic, tuberculous or lymphocytic choriomeningitis It has been found in suspected cases of brain tumor, subarachnoidal hemorrhage, brain abscess, encephalitis and subdural hematoma It has also been confused with various of the malignant lymphomas and in a surprising number of cases has been associated with one of the malignant lymphomas[8] In one of the cases studied at the Medical Center, the primary diagnosis of carcinoma of the prostate had been made Later the patient had Torula meningitis and at autopsy, the organism was found to involve the prostate as well as the remainder of the urinary tract No evidence of prostatic cancer was noted on tissue section (Case reported by Voyles and Beck[4])

The diagnosis of torulosis may be aided by skin biopsy when lesions are cutaneous, and by cultures of skin lesions, urine and spinal fluid Only rarely has the organism been isolated from the blood by culture[9] In the presence of Torula meningitis, examination of the spinal fluid will usually reveal the round or oval yeast like cells 5 to 6 microns in diameter surrounded by a large capsule Occasionally, budding forms may be seen, the organism does not form ascospores or mycelia Fresh India ink preparations with the spinal fluid are helpful in identifying the organism The organisms may be mistaken for red cells or lymphocytes The spinal fluid pressure may be normal and the fluid clear and colorless However, the pressure may be increased and the color slightly yellow The cell count generally contains an increased number of lymphocytes, on occasion polymorphonuclear cells predominate The protein content is generally elevated and the sugar and chloride determinations reduced significantly

Sabouraud's medium provides a compatible environment for the cryptococcus to grow The initial colonies usually appear in two to four days at room temperature Fermentation reactions of this organism as a basis for identification are quite unreliable The presence of a large gelatinous capsule seen in an India ink preparation differentiates this fungus from other yeast like organisms Reproduction is by budding No specific immune antibodies can be identified

Cryptococcus neoformans produces granulomatous reactions in the tissue Very few polymorphonuclear leukocytes are present The type of reaction occasionally is similar to that produced by foreign bodies The lesion resembles one caused by the tubercle bacillus but generally differs by the absence of caseation necrosis

The intracranial lesions of cryptococcosis may be meningeal or perivascular In the meningeal type the cerebral spinal fluid may be increased or decreased in amount, and the superficial veins are generally distended The meninges are thickened due to proliferation of fibroblasts and infiltration of lymphocytes, macrophages and plasma cells Variable numbers of multinucleated giant cells containing the yeast organism are often present In chronic cryptococcic meningitis the meningeal spaces are filled with clumps of fused macrophages, many containing great numbers of the yeast-like organism. There may be extension of inflammation along the vessels from the meninges into the cortex. Within the brain substance, there may be numerous spaces filled with a translucent colloid material which does not flow when the spaces are opened. These spaces may teem with yeast forms and yet show no evidence of inflammation. The cystic change is believed to be the result of embolism rather than due to a so-called histolytic substance in the capsule of the organism as was first supposed by Stoddard and Cutler. In the lungs and other organs the lesions produced are similar to those in the meninges.

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[8] Gendel, B R Ende, M and Norman, S L Cryptococcis, review with special reference to apparent association with Hodgkin's disease Am J Med, 9 343 355 1950

[9] Cox, L B and Tolhurst J C Human torulosis clinical and pathological and micro biological study, with report of 13 cases Melbourne Press, 1946

In all four cases examined post mortem at the Indiana University Medical Center, there was involvement of the brain and adrenal glands. Three of the cases demonstrated lesions in the lungs and kidneys. In only one case were there cutaneous lesions and in one case only was the spleen involved. In two of the four cases the organism was demonstrated in the prostate and in both of these cases the organism was isolated from the urine. All of the patients were men.

Vital statistics from the Indiana State Board of Health add at least three deaths occurring in the state due to systemic torulosis since 1949. This relatively "unlooked-for" infection probably occurs more frequently than is supposed, but the fact is not known because of the paucity of autopsies obtained in the general population. In addition, the disease is difficult to diagnose clinically and the presumed rarity is on that basis. In only one of the four cases autopsied at the Medical Center was the diagnosis made ante mortem.

In cases suspected of slowly developing brain tumors or chronic meningitis, (common diagnostic pitfalls), the physician should always consider a mycotic organism as the possible cause of the patient's symptoms. Mosberg and Arnold[5] state that torulosis should be suspected whenever unexplained cerebrospinal pleocytosis is present.

SUMMARY

This is a hitherto unpublished case of meningo-encephalitis due to Cryptococcus neoformans with lesions in the left adrenal and prostate. This case is unusual in two aspects because of the lack of lung involvement and the presence of infection of the prostate. This is the third such case reported with prostatic involvement. The total number of cases of systemic torulosis now in the literature is well over the two-hundred mark. It is hoped that with the addition of new cases to the literature from many areas the clinician will become more aware of cryptococcus infections and increase the frequency of recognition of this entity.

Pathology Department, Henry Ford Hospital, Detroit 2, Mich. (*H. E. B.*)

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PRIMARY BENIGN TUMORS OF THE EPIDIDYMIS WITH SPECIAL REFERENCE TO TUMORS OF UNUSUAL HISTOLOGIC CHARACTER SUGGESTIVE OF MALIGNANCY

JOSEPH A LAZARUS AND FRIEDRICH FRIEDMANN

Primary tumors of the epididymis, benign and malignant, although rare, have frequently been reported It is our purpose to briefly review the literature pertaining to the benign tumors in question, and to specially emphasize an intermediate group presenting histologic features which tend to make their true identity confusing and uncertain Pathologists, even after the most critical study of specimens falling within this category, cannot state with absolute certainty whether such tumors are completely benign or present so called mild malignant tendencies

In 1938 the senior author (J A L) collected 40 examples of primary malignant tumors of the epididymis, including one which he reported Since then, twelve additional cases have been reported In regard to the class of benign or apparently benign tumors, a cursory review of the literature disclosed approximately 50 cases

In 1947 Beneventi reported an example of a benign hard tumor of the epididymis grossly resembling a small fibroid, which, histologically, was shown to consist of interlacing strands or channels "lined with flattened, thin, cuboidal or even columnar epithelium in a fibrous tissue stroma"

Similar cases have been reported under various designations, such as adenoma (Blumer, Gordon Taylor), fibromyoma (Terrilon, Gordon Taylor), myo adeno fibroma (Fischer), epididymoma (Adams), mesothelioma (Evans, Masson, Baird, Robinson, Patterson and Mogg), leiomyoma (myoma) (Spivack, Foged, Friedman and Grayzel), lymphangioma (Marcandier, Baird), adenomatoid (Golden, Davenport, Burros and Mayock, Meeter), adenomyoma (Sakaguchi), mixed leiomyoma and lymphangioma (Halpert, Malisoff and Helpern), hemangioma (Dotta and Delporte), tumors simulating carcinoma (Stout), and adenocarcinoma (Thompson)

The only two examples of cholesteatomas were reported by Kundert in 1946 and by Pingree and Brown in 1951 The same year (1946) Sworn, Marshall and Edwards presented 2 cases of solid primary tumors of the epididymis which were adenomatous mixed tumors Two specimens of adenofibromyoma of the epididymis were described by Falconer in 1947 In 1949 Gallizia and Marazzini reported the condition of a patient who had bilateral leiomyomas of the epididymis, and similar cases were recorded by Foged and by Milner and Gilbert Glazer, in 1950, described two primary benign tumors of the epididymis, one he termed a "lymphangio epithelioma" and the other a "capillary hemangioma" Perez Castro described a tumor which he named "probable cystic embryoma" Morehead reported an angiomatoid tumor of the epididymis with extreme sclerosis of the fibromuscular tissue (1946) An example of adrenal cortical adenoma of the epididymis was described by Freeman in 1945

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Primary tumors of the epididymis are extraordinarily rare. Thompson, in 1936, collected 41 examples involving the spermatic cord, epididymis and testicular tunics, and of this number there were only 13 primary tumors of the epididymis. We have been able to collect 50 definitely benign tumors and five which were probably benign. According to Thompson, 40 per cent of tumors in his series were benign and 60 per cent malignant. Our data show a total of 50 definitely benign tumors and 5 probably benign as against 52 definitely malignant and one probably malignant.

In 1916, Sakaguchi removed a long-existent tumor from the epididymis of a 35-year old patient and categorized it as an adenomyoma. This apparently was the first report of such a tumor in the literature. Thompson's example was called cystadenoma. It was present in a 54-year old man who noticed a mass in the upper pole of the epididymis 25 years previously. An orchiectomy was accomplished but the testis was found to be normal. Up to 1936, only one lipoma of the epididymis was reported (Wildbolz).

Although myoma (leiomyoma) appears to be the most common benign tumor of the epididymis (8 cases, of which 3 were bilateral and 3 mixed), Rubaschow maintained that it should not be considered primary in the epididymis because it takes origin from contiguous tissue.

Hinman and Gibson, and also Rubaschow, maintain that there has been no authentic example of true fibroma of the epididymis reported in the literature. Since then, however, 1 case has been recorded (Bothe, Devers and Cristol). Thompson is of the opinion that all fibromas take origin in the caudal end of the spermatic cord and not in the epididymis. In 1911, Hardonin exemplified a tumor which he classified as angioma, and Dotta and Delporte (1941) presented one which they considered to be an hemangioma of the epididymis. Specimens of lymphangiomas were shown in 1925 by Rigano-Irrera and also by Marcandier and Thomas in 1930. An example of mixed tumor consisting of leiomyoma and lymphangioma was reported by Halpert (1941). Four tumors of vascular origin were demonstrated by Thompson from the Mayo Clinic (1 angioma, 2 hemangiomas and 1 lymphangioma). For the first time in surgical annals he also showed a dermoid cyst of the epididymis. Martin and Sermet, in 1932, described two tumors which they called benign cystic embryomas.

Rubaschow maintained that tumors of the epididymis may arise from 1) cells of the epididymal tubules; 2) the wolffian or myotome anlages, and 3) adjacent stromal tissues, such as blood or lymph vessels, fat, fibrous tissue, etc.

The difficulty in differentiating between inflammatory lesions of the epididymis and true neoplasms has been clearly emphasized by Stout. He believes distortion of ducts of the epididymis may, at times, simulate cords, channels, and cell masses which in turn closely mimic malignant tumors. Mucus may, at times, be produced by epithelial cells within these cords, resulting in formation of cysts. It is not unusual in these atypical inflammatory lesions to see clumps of epithelial cells which are not enlarged, stain deeply and occasionally show mitotic figures. These tumors have often been diagnosed as malignant.

Stout reported a very interesting example of the difficulty involved in making a differential diagnosis between a benign and malignant tumor of the epididymis.

During the course of a laparotomy he found a mass which he attributed to an aggregation of carcinomatous lymph nodes compressing the common and cystic ducts and adherent to the hepatic flexure of the colon Because it was known that the patient had a solitary nodule in the tail of the epididymis, it was thought that the epididymal tumor represented the primary lesion and that the abdominal lymph nodes were metastatic The tumor was removed from the epididymis and subjected to frozen section histologic study Interlacing strands of smooth muscle fibers and connective tissue were revealed and a number of irregular tubules lined with swollen cuboidal cells resembling adenocarcinoma, which was the conclusive diagnosis Five days later the patient succumbed from pneumonia On autopsy, a primary adenocarcinoma of the choledochus was discovered Additional sections taken from the epididymal tumor showed that what resembled epithelial lined tubules were actually blood and lymph vessels lined with swollen prominent endothelial cells The remainder of the tumor consisted of smooth muscle and connective tissue The final diagnosis was fibromyoma

Despite the many names which have been applied to tumors in this category, a critical study of the gross and histologic features discloses the fact that they all present similar general characteristics They are usually small, firm, well circumscribed nodules with a sheen which gives the impression that they are fibromas or fibromyomas On microscopic examination they disclose bundles of hypertrophied muscle fibers with intervening strands of connective tissue and clumps of epithelial cells arranged as solid cords or tubes lined with pale staining vesicular cells At times the lumina of the tubes appear dilated and the lining cells become flattened so that they resemble angiomas or lymphangiomas A characteristic feature of these cells is the clearcut nuclear membranes and nucleoli, and the vacuolated and pale cytoplasm Mitotic figures may at times be seen, which add to the difficulty of making a correct differential diagnosis

In 1943, Mackay reported two tumors which, although he failed to name them, presented the same physical characteristics as the one about to be described by us Codneie and Flynn described three tumors which they designated "adenomatoid tumors," but failed to maintain whether they were benign or malignant A similar name was ascribed to a tumor reported by Davenport in 1948, and another by Meeter in 1951, and also one by Falk and Hornwaler A tumor consisting of leiomyoma and lymphangioma was called "adenomatoid leiomyoma" by Wilson (1949), and the following year an adenomatoid tumor of the epididymis was found in a newborn child (Burros and Mayock)

CASE REPORT

Mr J W , 70 years of age, well nourished, a furrier by trade, consulted us February 2, 1952 because of a firm nodule in the area of the right testis, which had first made its appearance 1 year previously Five years ago he was examined by us because of pain in the back The only abnormality found was a moderately enlarged prostate The testicular nodule had shown some slight enlargement during the past few weeks Aside from a slight dragging sensation in the right scrotum, there was no pain, weight loss or other suggestive symptoms

Physical examination disclosed a well developed, healthy looking man, weighing 201 pounds. The sole outstanding feature of the examination was found in the right scrotum which presented a round, firm, nontender nodule about the size of a cherry involving the tail of the epididymis. The testis itself was unaffected. There was no beading of the vas. The prostate was moderately enlarged and elastic, and the vesicles felt normal. Laboratory and roentgen studies revealed nothing abnormal.

Operation (February 17, 1952): Under spinal and sodium pentothal anesthesia the right epididymis was dissected free of the testis. The tumor, situated in the tail of the epididymis, was firm and completely encapsulated, and on cut surfaces appeared glistening and yellowish-white. It was removed and submitted for frozen section. From the gross appearance the pathologist was of the opinion that it was a benign fibroma. The report of the frozen section was "Specimen consists of a well encapsulated, firm, spheroid tumor mass removed from the epididymis of the right testis as an extirpation biopsy. It measures 3.5 cm. in diameter, presents a thin, intact capsule and cuts with marked resistance. The cut surface resembled that of a hard fibroma. Selected areas studied from frozen section show small cords and alveoli of large vacuolated epithelial cells with large nuclei. Diagnosis: Adenocarcinoma of undetermined origin."

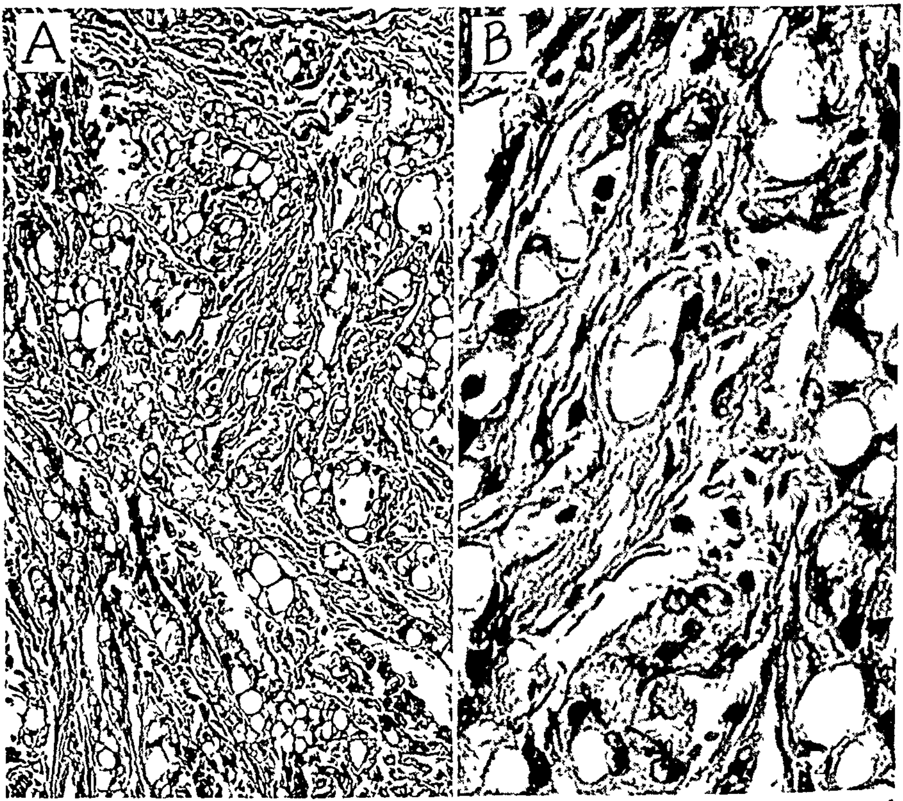

FIG. 1. *A*, note dense fibrous network consisting of islands of cellular tissue with clearly defined lumina (× 130). *B*, lumina, lined with one layer of flat to cuboidal epithelial cells are clearly seen. Note fibro-adenomatous network surrounding lumina with no mitotic figures discernible (× 535).

For this reason a right orchiectomy and high excision of the spermatic cord were accomplished

Final pathologic report "Microscopic studies of epididymal tumor show a fibroleiomyoma in which there are numerous infiltrating cords and groups of cells having the characteristics of well developed vacuolated endothelial cells of lymph vascular origin The diagnosis made on frozen sections is therefore changed to that of lymphangiosarcoma of low grade malignancy Final diagnosis· Tumor of right epididymis Fibroleiomyoma with lymphangiosarcoma (low-grade malignancy) " See figure 1

Report on right testis and spermatic cord "Focal atrophy of seminiferous tubules with reduced spermatogenesis

"Epididymis and cord focal fibrosis and slight arteriosclerosis No evidence of tumor extension or metastases "

The patient made an uneventful recovery, and when last seen, April 18, 1952, appeared in excellent condition

Although the pathologist's final diagnosis was "fibroleiomyoma with lymphangiosarcoma of low grade malignancy," a careful study of the microscopic section disclosed features which are so characteristic of this entire category of tumors, that it is our belief that the tumor is clinically benign and should fall within that category

DISCUSSION

While primary tumors of the epididymis, benign or malignant, are rare, it may be maintained that the benign variety is extremely rare There is one uncommon group of tumors which have been described under various names, and even on occasion have been described as presenting evidence of low grade malignancy On careful scrutiny, however, these tumors reveal a general histologic pattern which makes them distinctive histologic entities They are firm, discrete, well circumscribed and encapsulated lesions arising in the epididymis and never invading the testis On cross section they present a glistening appearance and have all the outward appearance of a benign fibroma or fibromyoma A more intensive study of the histologic slides, however, shows them to consist of bundles of muscle and fibrous tissue and nests of epithelial cells arranged as solid or hollow cords lined by large nucleated pale staining cuboidal cells The cells, when lining the hollow cords, show greater dilatation, become flattened and resemble endothelial cells lining angiomas or lymphangiomas While mitoses are usually absent, a few mitotic cells may be present Depending upon the predominance of one or another of the various structures that make up these tumors, they have been designated variously, such as adenomas, fibromyoma, myo adenofibroma, mesothelioma, lymphangioma, and even adenocarcinoma

CONCLUSIONS

We report the case of a 70 year old patient who presented a solid, small, well encapsulated tumor of the right epididymis which, on gross section, was first reported as a fibroma, on frozen section an adenocarcinoma, and finally on paraffin section as fibroleiomyoma with lymphangiosarcoma of lowgrade malignancy. However, comparing the gross and microscopic features of this tumor with others reported as benign primary tumor of the epididymis, we believe that this tumor may and should be grouped with the series of an extremely rare one of primary tumors of the epididymis which we have described as of a questionable degree of malignancy. A review of the available literature shows only 50 cases of definitely benign tumors, exclusive of the one here presented, and 5 probably benign.

875 Park Ave., New York 21, N. Y.

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RENAL PAPILLARY NECROSIS

DAVID SWARTZ

Renal papillary necrosis, variously known as renal papillitis, medullary necrosis, papillitis necroticans and necrotizing papillitis, is an ischemic necrotic lesion of the renal papillae which may be encountered in diabetic patients although it may also occur in non diabetic patients with chronic urinary obstruction The vast majority of cases reported in the literature were discovered at autopsy Two cases herewith reported were advanced unilateral renal lesions in diabetic patients who recovered following nephrectomy One other, a non diabetic infant was discovered at autopsy

The first description of this condition dates back to 1877 when Friedreich[1] reported a case of a man aged 70 who had prostatic disease, hydronephrosis and bilateral papillary necrosis The association of papillary necrosis and diabetes mellitus was first emphasized by Gunther[2] in 1937, who brought the condition to medical attention More recent reports by Harrison and Bailey,[3] S L Robbins et al ,[4] Edmondson et al ,[5] Robbins and Angrist,[6] Muirhead et al ,[7] and others indicate the magnitude of this problem

CLINICAL MANIFESTATION OF PAPILLARY NECROSIS

In lesions that develop on an obstructive basis the clinical manifestations are primarily those of the condition giving rise to obstruction, in the majority of cases prostatic hyperplasia associated with severe infection and renal damage Superimposed upon this is a terminal acute inflammatory episode

In diabetic patients the clinical manifestations are divided into an acute[4] and a subacute variety The severity of the symptoms are dependent upon the extent of the lesion In the acute variety, there is rapid onset of illness with chills, fever, prostration, rapid pulse, leukocytosis and coma Urinary findings consist of pyuria, hematuria and oliguria Death is due to infection and uremia In the subacute variety the patient gives a history of prolonged pyelonephritis with remissions and exacerbations The diabetic state is difficult to control and the patient may lapse into coma Ureteral colic may be a feature This is produced by the passage through the ureter of pieces of necrotic tissue The sudden development of severe diabetic acidosis, a rising blood urea and general deterioration portend the onset of the terminal state

Pyelographic findings are the result of destruction of renal papillae[8] The lesion may simulate renal tuberculosis or advanced non tuberculous pyelonephritis A

Read at annual meeting of the Canadian Urological Association, Niagara Falls, Ontario, June 6 1952

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moth-eaten appearance of the minor calyces results from necrosis and sloughing of the renal papillae. In advanced cases with peripheral excavation the extravasated contrast medium extends into the renal cortex. Dilatation may be so pronounced as to suggest cavern formation. A portion of a pyramid which has sloughed away and floats free in the renal pelvis may cast a negative shadow suggesting a non-opaque stone.

BACTERIOLOGY

A great variety of bacterial agents have been isolated in these cases. The commonest offender is Escherichia coli. Other organisms noted in several of the reported cases are Staphylococcus aureus, Klebsiella pneumoniae (Friedlander's bacillus), Bacillus proteus, alpha and beta streptococci and Pseudomonas aeruginosa. Welch and Prather[9] reported a case of pneumonephrosis complicating necrotizing papillitis. In their review of the literature of pneumonephrosis they state that a more complete case history and interpretation would no doubt place some of these cases in the same category as the one they have reported. In these cases the organisms mainly at fault are Esch. coli, Bacillus lactis aerogenes and Bacillus aerogenes capsulatus.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis the following conditions should be considered:

1) *Renal tuberculosis:*—The pyelographic similarity may lead to some confusion.

2) *Acute destructive pyelonephritis in diabetic patients without papillary necrosis:*—The patient is rarely as ill and the course less severe. While pyelograms may be diagnostic in some cases they are not in all. The response of this condition to conservative measures may rule out the more serious lesion.

3) *Renal tumors:*—In those cases of papillitis associated with gross hematuria, there may be some difficulty in ruling out renal tumor.

4) *Renal colic associated with calculus:*—The passage of pieces of necrotic tissue may give rise to ureteral colic and resemble lithiasis.

TREATMENT

The principles concerning prevention should be observed: 1) Careful control of the diabetic state and frequent search for urinary infection may prevent this serious complication. 2) The appropriate surgical care of obstructive uropathy will prevent this condition in the aged.

Treatment proper is that of urinary infection. The appropriate chemotherapeutic or antibiotic agent or both are administered, following thorough investigation. In the 2 surgical cases described nephrectomy was justified on the basis of an advanced unilateral renal lesion with massive destruction and gross infection. The remaining kidney in each case was free of infection and pyelographically normal. There are other recorded cases in which nephrectomy was performed. In the two surgical cases reported by Robbins, S. L. et al.,[1] the patients were alive and well a year later. Of three such cases reported by Gunther,[2] two

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[9] Welch, N. M. and Prather, G. C.: J. Urol., **61:** 712, 1949.

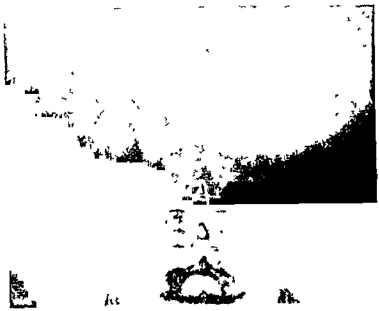

FIG. 1. Case 1. Excretory urogram (August 1950) prior to development of necrosis. Left kidney structurally normal but concentration is diminished.

survived. Bilateral lesions have proved fatal in the reported cases. That necrotic renal pyramids can go on to healing has been demonstrated in autopsied cases reported by Robbins[6] and Angrist,[5] Edmondson et al. and Gunther.[2] Tissue damage however has been so great as to negate the possible curative effects of this phenomenon.

CASE REPORTS

Case 1. Mrs. E. A., a 63 year old woman, para 4, grava 4, had been treated for diabetes mellitus for 14 years. Her diabetic state was difficult to control, having had one episode of coma early in 1950. In August 1950, she was urologically investigated because of persistent pyuria and left loin pain. Excretory urogram August 24, 1950 (fig. 1) showed both kidneys to be normal structurally although the left kidney did not concentrate as well as the right. Urinary culture revealed Esch. coli and Strep. fecalis. Her blood pressure ranged from 250/130 to 220/100. Eye grounds showed bilateral chorioretinosis typical of diabetes, and retinal arteriosclerosis. She first came to my attention in December 1950, because of persistence of constitutional symptoms, left loin pain and pyuria. Cystoscopic examination revealed a mild degree of cystitis, both ureteral orifices being normal. Specimen of urine from the right kidney was crystal clear and free of pus; that from the left kidney was turbid and loaded with pus cells. Smear, culture and guinea pig inoculation of left kidney urine were negative for tubercle bacilli. Retrograde pyelography January 29, 1951 (fig. 2): the right kidney was structurally normal. The left kidney showed typical changes characteristic of papillary necrosis. Excretory urogram February 5, 1951 showed a normal right kidney and a poorly functioning left kidney. On February 9, 1951, a left nephrectomy was performed, followed by an uneventful recovery. At present more than 2 years following surgery her general health has improved considerably, there is no evidence of urinary infection and her diabetic state is easier to control.

Pathological report: Specimen (fig. 4) consisted of a kidney measuring 10.5 by 6 by 5 cm. and weighing 203 gm. The capsule stripped with moderate ease

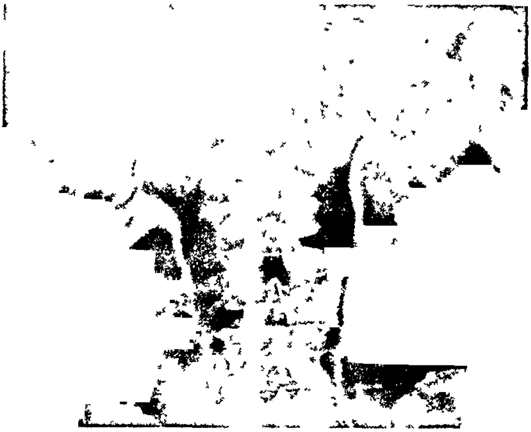

Fig. 2. Case 1. Retrograde left pyelogram (January 1951). Upper pole shows cavitation extending into cortex. Negative shadows produced by sequestrated necrotic papillae. Crescentic shadows are formed by contrast medium lining detached necrotic substance.

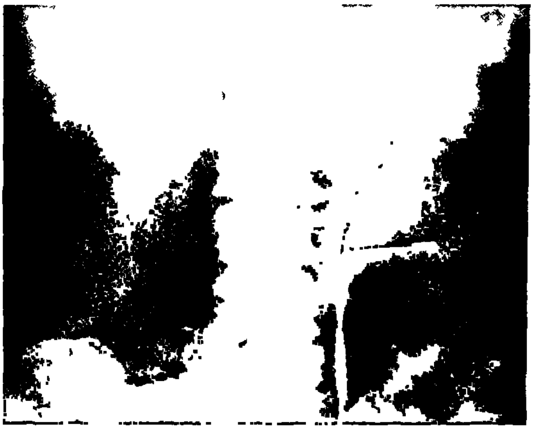

Fig. 3. Case 2. Retrograde left pyelogram (May 1951). Incomplete filling and moth eaten appearance of calyces are produced by papillary necrosis.

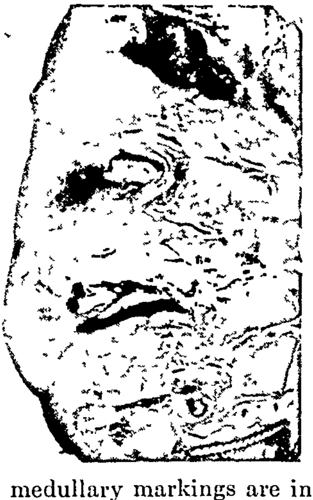

Fig. 4. Case 1. Cortical and medullary markings are indistinct. Necrotic papillae are separated from base of pyramids by inflammatory zone. Necrotic papillae appear in various states of detachment. Cavities are formed by complete sequestration of papillae. Patent interlobar vessels whose walls are not grossly thickened are noted alongside pyramids.

leaving a glistening finely granular but coarsely scarred surface The cortical and medullary markings were indistinct The cortex measured up to 0 6 cm in thickness, and the medulla up to 1 5 cm Several, but not all the papillae were an opaque *yellowish color, moderately soft in consistency,* and were separated from the base of the pyramids by an arc-like zone of hyperemia One papilla had become completely separated from its base, and lay free within its calyx as a soft yellowish concretion The pelvis was not dilated, but the mucosa was hyperemic and had a finely granular surface The walls of small arteries in the pelvis appeared thickened

A description of the microscopic appearance is omitted because of its similarity to case 2

Anatomic diagnosis Chronic pyelonephritis, renal papillary necrosis, arterial and arteriolar nephrosclerosis

Case 2 Mrs F McD , aged 65, was admitted to Victoria Hospital, Winnipeg, May 2, 1951 She had been treated for 12 years for diabetes mellitus which during the past year had been difficult to control She complained of pain in the left loin, frequency, dysuria and general malaise Examination revealed a tender mass in the left loin, a swinging temperature, gross pyuria and glycosuria, and gram negative bacilli were present in the urinary sediment Smears and culture were negative for tubercle bacilli Blood pressure ranged from 220/110 to 160/90 Excretory urography revealed a normal right kidney while the left kidney did not visualize On cystoscopy May 12, 1951, there was nothing remarkable about the bladder Specimen of urine from the right kidney was clear and free of pus, that from the left kidney was turbid, loaded with pus cells and culture revealed Esch coli Left retrograde pyelogram (fig 3) revealed changes due to papillary necrosis On June 9, 1951 a left nephrectomy was performed Because of perinephritis and massive adhesions this was done subcapsularly She made a good recovery and was discharged from hospital June 22, 1951 She died 3 months later of a cerebro vascular accident

Pathological report Specimen (figs 5 and 6) consisted of a kidney measuring 12 2 by 6 by 5 5 cm , and weighing 250 gm The perirenal fat attached to the capsule measured up to 0 7 cm in thickness and appeared somewhat indurated The capsule stripped with moderate ease, leaving a relatively smooth surface The cortical and medullary markings were indistinct The pelvis was not dilated but the mucous membrane had a finely granular appearance Most of the papillae appeared grossly necrotic, friable and of an opaque yellowish color One pyramid was still attached to its non necrotic base, and the non-necrotic base exhibited some degree of hyperemia Other necrotic papillae were partially or completely detached One separated necrotic papilla still lay within the calyx, but other papillae were absent, and the mucosa of the resulting dilated calyces had a finely granular appearance The interlobar vessels alongside the pyramids were patent and their walls did not appear grossly thickened

Microscopic *appearance (figs 7 8, 9, 10, 11 and 12)* The *affected renal papillae* were completely necrotic Cell outlines were not distinguishable but radiating outlines of collecting tubules were still apparent A broad zone of polymorphonuclear infiltration was present at the junction between the necrotic and still viable

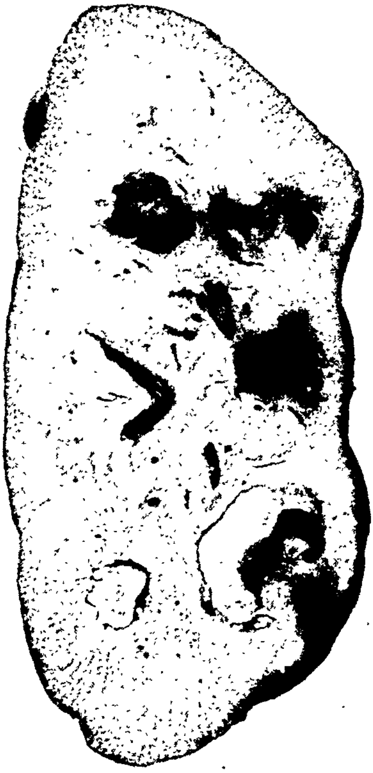

FIG. 5. Case 2. Appearance on gross examination identical with specimen removed in case 1 (fig. 4).

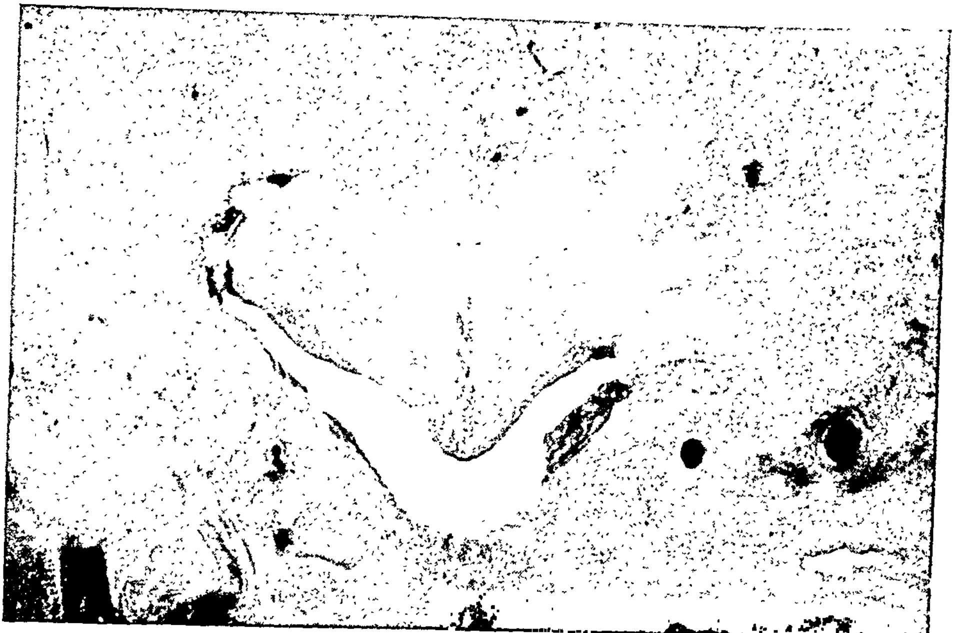

FIG. 6. Case 2. Partially detached necrotic papilla projecting into calyx

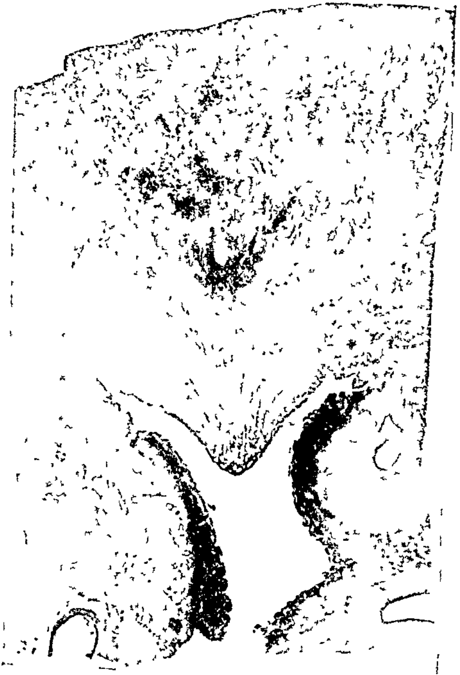

FIG. 7. Case 2. Low power. Necrotic papilla showing inflammatory infiltrate at its base and inflammatory calyceal lining

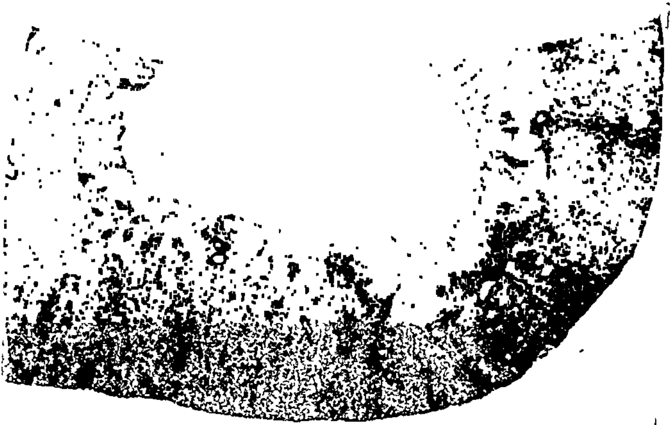

FIG 8 Case 2 Low power Papilla has completely sloughed away and cavity is lined by inflammatory infiltrate.

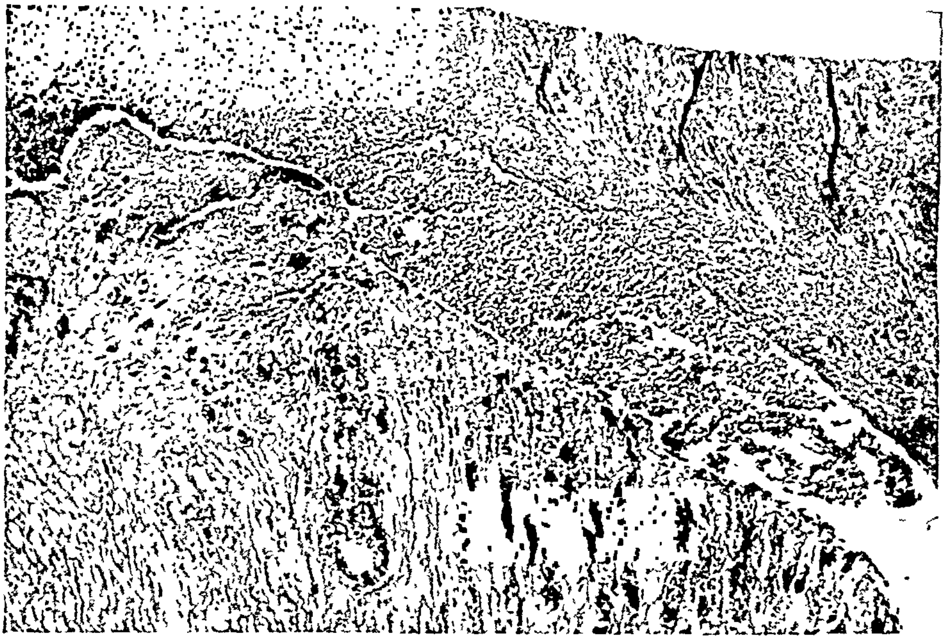

FIG. 9. Case 2. Low power. Necrotic papilla shows tubular outlines but no cell outlines. Heavy infiltrate of polymorphonuclears between necrotic and non-necrotic tissue. An infiltrate of plasma cells and lymphocytes is present in non-necrotic base.

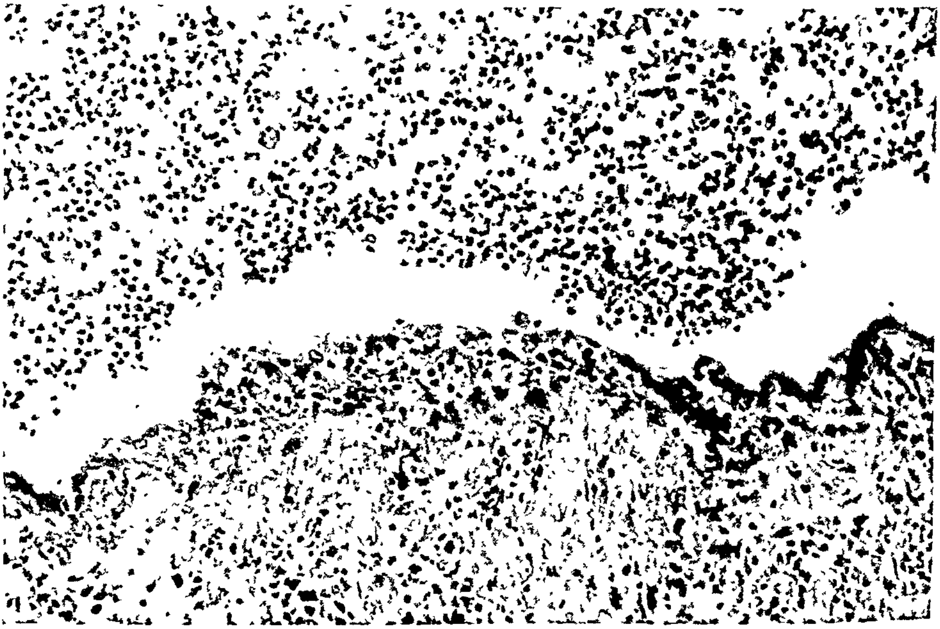

FIG. 10. Case 2. Low power. Epithelilization following separation of necrotic papilla indicating healing process.

portions of the papillae and in some areas this purulent inflammatory exudate extended almost to the arcuate vessels. Nonspecific granulation tissue separated the necrotic portion of the pyramid from the viable portions and in some areas was clothed by a single layer of epithelium indicating a healing process. Scattered

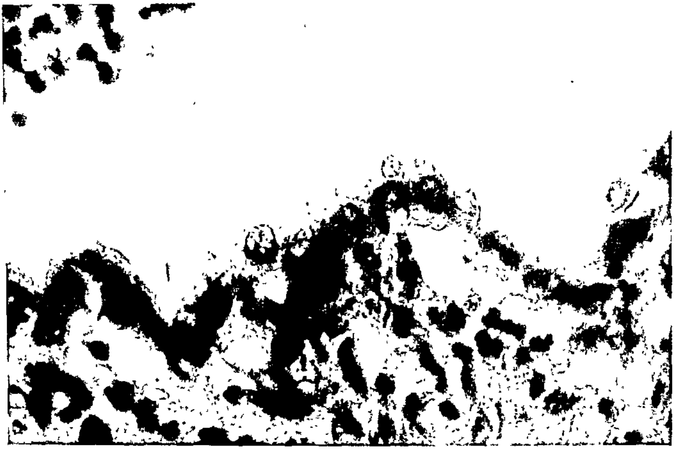

FIG. 11. Case 2. High power. Epithelialization as in figure 10

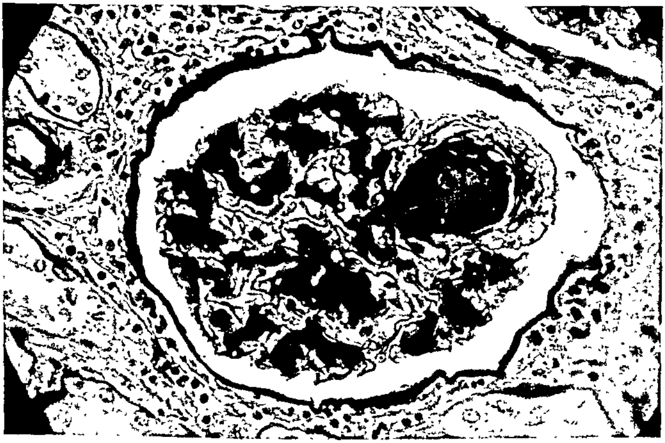

FIG. 12. Case 2. High power. Diabetic glomerulosclerosis. Focal and nodular hyalin thickening of capillary basement membrane. Thickening of parietal layer of Bowman's capsule.

throughout the interstitial connective tissue of the kidney and the pelvic mucosa was a heavy infiltrate of lymphocytes and plasma cells.

Varying degrees of diabetic nodular sclerosis were present, particularly well demonstrated with the McManus stain. The arteriolar walls exhibited hyalin thickening and there was a moderate, though not pronounced thickening of the parietal layer of Bowman's capsule. Varying and prominent degrees of arteriosclerosis were present within the renal, interlobar and arcuate arteries. The small capillaries in the interstitial tissue between the straight tubules were identified with difficulty because of the inflammatory infiltrate, but where identity could be established with certainty these vessels appeared completely normal and exhibited no evidence of thrombosis.

Anatomic diagnosis: Chronic pyelonephritis; renal papillary necrosis; diabetic nodular glomerulosclerosis.

Case 3. Baby girl J. S. was a healthy infant until 5 months of age, then failed to develop normally. At the age of 15 months she was admitted to the Children's Hospital, Winnipeg because of persistent fever of unknown origin ranging from 103 to 108F. An exploratory craniotomy was performed because of suspicion of a subdural hematoma but at operation there was no hematoma, only diffuse cerebral atrophy.

Autopsy revealed an early Pseudomonas aeruginosa meningitis, moderate cerebral atrophy and other intracranial findings whose etiology is not understood. Bilateral renal papillary necrosis was discovered although not suspected during life.

The right kidney weighed 41.5 gm., and the left 42 gm. The capsule stripped with ease leaving a smooth glistening surface. The cut surface exhibited a remarkable appearance. The renal papillae were yellow in color and grossly necrotic. There was an arc-like zone of hyperemia at the base of the pyramids which did not extend to the corticomedullary junction. The corticomedullary junction was distinct. The cortex, in contrast to the midportion of the medulla, exhibited no

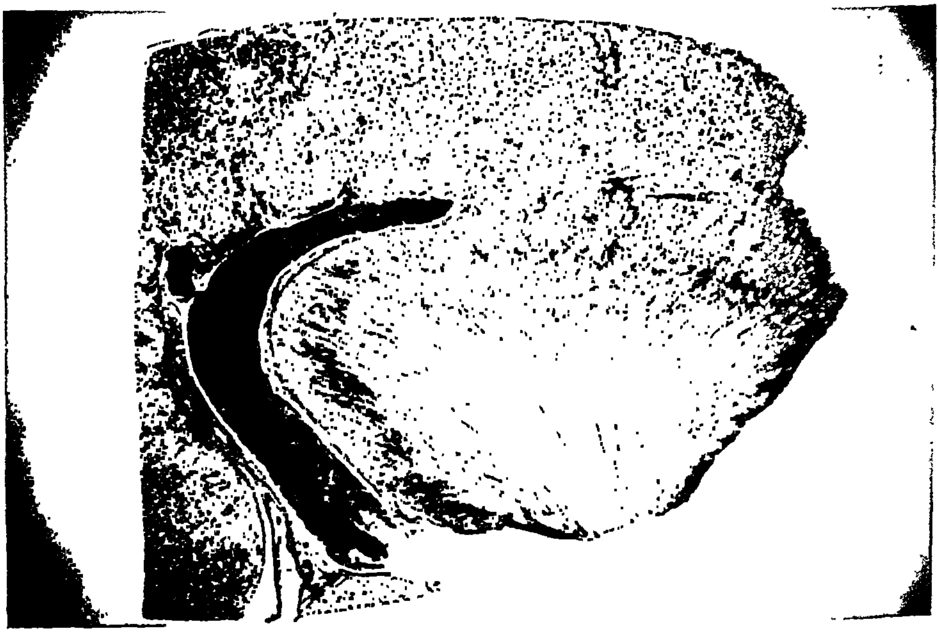

Fig. 13. Case 2. Necrosis occupies cone-like central position within papilla extending to its tip. Hemorrhagic zone lines necrotic portion. Interlobar, arcuate and intralobular veins are distended with fibrin thrombus.

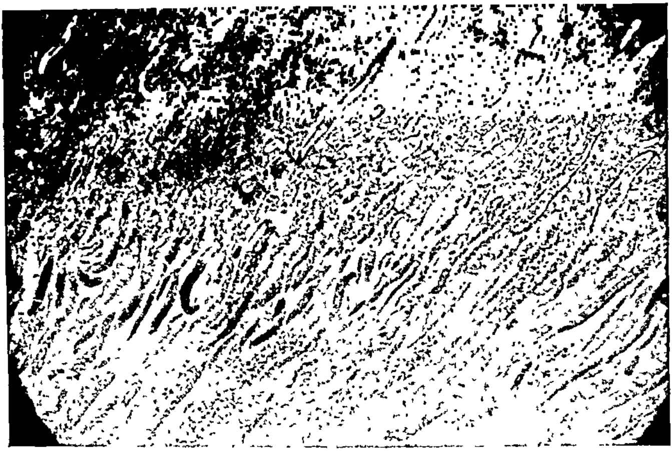

FIG. 14. Case 3. Low power. Necrotic papilla revealing tubular but absence of cell outline. Numerous red blood cells and distended capillaries are present, but no inflammatory exudate.

evidence of hyperemia. Close inspection revealed small, firm, white thrombi within the interlobar veins measuring 1 mm. in diameter. These did not extend into the main renal vein or branches thereof. The pelvis was not dilated and mucous membrane pale, smooth and glistening. The renal arteries and interlobar arteries were patent and normal.

Microscopic appearance (figs. 13, 14, and 15): All the renal papillae exhibited recent necrosis. The tubular outlines were still visible but the cells appeared only as faint eosinophilic outlines.

There was still a thin rim of viable tubules at the periphery of the papillae, and the necrosis reached to within 1 to 2 mm. of the arcuate vessels. The necrosis occupied a cone-like central position within the papillae, and extened to the tips of the papillae. There was hemorrhage into the interstitial tissue at the edges of the necrotic portions, the capillaries between the straight tubules were distended, and many contained amorphous eosinophilic thrombi. The interlobar veins were greatly distended and filled with antemortem fibrin thrombus, which extended for a short distance into the intralobular veins. Despite the hemorrhage and congestion within the medulla, there was a remarkable lack of vascular congestion within the cortex.

Nowhere was there any inflammatory infiltration. There was no inflammatory infiltrate within the necrotic areas, at the edges of the necrotic papillae, in the pelvic mucosa, or within the interstitial tissue of the renal parenchyma. There was no inflammatory infiltrate within the walls of the interlobar vessels, though there were numerous leukocytes enmeshed within the fibrin thrombi. The remaining renal parenchyma was completely normal, and there was no evidence of toxic degenerative change within the tubular epithelium.

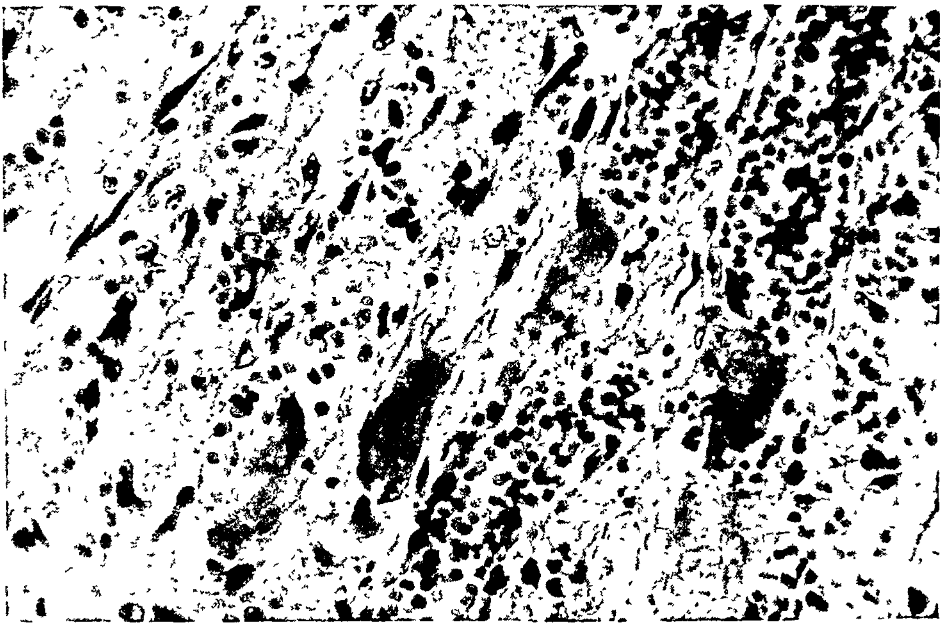

Fig. 15. Case 3. High power. Capillaries distended with red blood cells and thrombi and hemorrhage into interstitial tissue.

PATHOGENESIS

The classical pathology of renal papillary necrosis, as reported in the literature, is exemplified in the resected kidneys of cases 1 and 2. Numerous theories have been advanced regarding the pathogenesis of this lesion, and these have been adequately reviewed by Sheehan[10] (1937), Edmondson et al.[5] (1947), and Robbins and Angrist[6] (1949). Most observers agree that the essential pathological feature of this disease is ischemic necrosis, anatomically localized to the renal papillae, but the mechanism whereby this is produced is under some doubt.

In diabetics, pyelonephritis is a constant accompanying lesion of papillary necrosis, and where adequate clinical studies have been performed, it is evident that pyelonephritis actually precedes for some time the occurrence of papillary necrosis. Histological evidence also indicates that pyelonephritis has preceded the advent of this complication.

As pyelonephritis and urinary tract obstruction are also an almost but not invariably constant accompaniment of papillary necrosis in non-diabetics, it has been tempting to assume that the severity of the inflammatory infiltrate within the interstitial tissue at the base of the pyramids compromises the circulation through these areas to such an extent, that necrosis of the distal portion of the papillae results.

It is apparent, however, as observed in case 1, that the presence or absence of necrosis may not depend entirely on the degree of inflammatory infiltration, for the bases of nonnecrotic pyramids contained as extensive an inflammatory infiltrate, as the bases of the necrotic papillae. Moreover, Sheehan[10] has observed a patient with bilateral papillary necrosis, whose only renal inflammatory lesions were a few tiny microscopic abscesses confined to the cortex.

Case 3 has been included in this report to illustrate the occurrence of renal papillary necrosis in the absence of inflammatory disease of the kidney, and in this example one might assume that the papillary necrosis was subsequent to the venous thrombosis. The vascular dilatation, congestion, and hemorrhage in the necrotic and nonnecrotic portions of the medulla appear to substantiate this assumption.

The cone shaped necrosis within the centers of the papillae may be a significant clue regarding the vascular supply of the papillae, for if the necrosis is due to vascular occlusion, it is evident that the peripheral portion of the papilla must have either a different or additional vascular supply or drainage to that of the central portion. It is perhaps also significant in this regard, that this same cone-shaped central necrosis occurs in the diabetic patients.

Although the gross and histological evidence in case 3 suggests that necrosis was due to venous occlusion absolute acceptance of this interpretation must be made with some caution. Renal and intrarenal vein thrombosis is not too uncommon in infants (Zuelzer)[11] without evidence of necrosis. When necrosis does occur it is not usually confined to the renal papillae as in this case. Moreover the papillary necrosis reported by Sheehan[10] was associated with neither vascular occlusion nor inflammatory disease. In cases such as these, it is evident that factual evidence is at present insufficient to explain the pathogenesis of this necrotic lesion without incurring purely theoretical and as yet unsubstantiated hypotheses. Such considerations include the role of vascular spasm, smooth muscle spasm within the papillae and calyces, or the action of hypothetical toxic substances upon the papillary tissue or vasculature.

Cases 1 and 2 present histological evidence of re epithelialization suggesting a healing process.

SUMMARY

Three cases of renal papillary necrosis are reported, two surgical cases in diabetic patients and one autopsied case in an infant.

Clinical manifestations, pyelographic findings, bacteriology, differential diagnosis and treatment are outlined.

The pathogenesis of papillary necrosis is discussed in some detail. This condition may occur in three forms 1) most commonly in association with pyelonephritis, 2) with vascular occlusion unassociated with pyelonephritis, 3) as an isolated lesion associated with neither renal inflammation nor vascular occlusion.

The conclusion is drawn that factual evidence is at present insufficient to fully explain the pathogenesis of every form of this lesion.

Appreciation is expressed to Dr. Jan Hoogstraten, pathologist to the Grace and Children's Hospitals, Winnipeg, for his assistance in the preparation of photographs, and pathological descriptions and discussions included in this paper.

332 Medical Arts Bldg., Winnipeg, Manitoba, Canada

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[10] Sheehan H L Lancet, 2 187 1937

[11] Zuelzer W W et al A M A Am J Dis Child, 81 1, 1951

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NEPHROCALCINOSIS: A COLLECTIVE AND CLINICOPATHOLOGIC STUDY

JD MORTENSEN AND JOHN L. EMMETT

Mayo Foundation and Section of Urology, Mayo Clinic, Rochester, Minn.

Deposits of calcium salts in renal parenchyma are well-known pathologic lesions, evidently being demonstrable histologically to some degree in from 5 to 25 per cent of all kidneys subjected to careful postmortem examination. Since 1855, when Virchow reported his observations on "Kalk-metastasen," an extensive bibliography has accumulated concerning the pathologic features and pathogenesis of this type of renal calcification in pathologic specimens. Clinical demonstration of diffuse renal calcification in the living patient, however, was not reported until 1934 when Albright and associates described the roentgenographic manifestations of calcium deposits in the kidneys of patients with primary hyperparathyroidism and coined the term, "nephrocalcinosis," to designate this renal lesion. Subsequently a considerable bibliography has accumulated on this subject. Information on clinically recognizable nephrocalcinosis, however, has not been collected or classified and is still largely dispersed in individual case reports. Therefore, we have undertaken a clinicopathologic study, the purpose of which was to collect, classify and analyze all available data pertaining to the roentgenographically demonstrable deposits of calcium in the kidneys. This communication is comprised of selected data, concepts and interpretations derived from the original, more exhaustive study.

At the outset we wish to make it clear that the data we have collected and the conclusions we present pertain only to renal calcification which is extensive enough to be demonstrable roentgenographically, hence only to clinically recognizable nephrocalcinosis.

TERMINOLOGY

The term, "nephrocalcinosis," is being used in current medical literature with various meanings and implications. Allen gave it a pathologic basis when he wrote that the term refers to histologically demonstrable renal calcification. On the other hand, Bell implied clinical recognizability when he stated that nephrocalcinosis means roentgenographically demonstrable renal calcification. Philologically the term simply denotes calcium in kidneys. It is evident that renal deposits of calcium may and do exist with considerable variation in size, number, density and extent, from a single Randall's plaque or an occasional calcified glomerulus to extensive impregnation of renal tissue with calcium salts or widespread destruction of renal parenchyma by large calcareous deposits. Definition of the term, "nephrocalcinosis," thus seems to constitute an arbitrary agreement

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Abridgment of thesis submitted by Dr. Mortensen to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

Read at meeting of North Central Section, American Urological Association, Minneapolis, Minn., October 9, 1952.

as to whether the term should be used to refer to any and all renal deposits of calcium or be reserved for a particular distribution, extent, or type

For our purposes, in this paper, we prefer to designate pathologically demonstrable renal deposits of calcium by the rather nonspecific term, "renal calcification " We have arbitrarily reserved the term, "nephrocalcinosis," to signify only that degree or type of renal calcification which is clinically recognizable by its characteristic roentgenographic manifestation Hence, in agreement with Bell, we have defined nephrocalcinosis as roentgenographically demonstrable diffuse renal parenchymal calcification

MATERIALS AND METHODS OF STUDY

We have obtained data pertaining to nephrocalcinosis, first by collecting from the medical literature all individual cases reported in which this lesion was demonstrated roentgenographically This source, to January 1, 1952, yielded satisfactory and reasonably complete reports on 48 patients To augment this series, we obtained records of 43 additional cases of roentgenographically demonstrated nephrocalcinosis studied at the Mayo Clinic prior to January 1, 1952 Roentgenographic, clinical and pathologic data derived from study of these 91 collected cases form the basis for this study

ROENTGENOGRAPHIC MANIFESTATIONS

The roentgenographic appearance of nephrocalcinosis in most instances is so striking and characteristic that little confusion or question exists as to the nature of the lesion Diffuse clusters of stippled shadows appear to lie in the medullary portions of the kidneys, usually collected primarily in the pyramids at the tips of the calyces Although there is remarkable similarity in the appearance of the lesion from case to case, we have recognized three variations, which we have arbitrarily designated "types A, B and C" (fig 1) Type A occurred in 66 per cent, type B in 19 per cent, type C in only 4 per cent and intermediary forms, not definitely classifiable as type A, B or C, in 11 per cent of the 91 collected cases

ASSOCIATED CAUSATIVE DISORDERS

Except in rare instances nephrocalcinosis is obviously a secondary manifestation of an underlying primary causative disorder That the specific causative disorder can be recognized in most cases is indeed fortunate, in contrast to our relative inability to recognize the cause of renal lithiasis in most cases Study of the 91 collected cases of nephrocalcinosis revealed that definite associated causative disorders were demonstrated in 83 5 per cent (fig 2) Three disorders accounted for three fourths of the cases studied These three important causes of nephrocalcinosis were primary hyperparathyroidism, hyperchloremic acidosis and chronic pyelonephritis Other causative disorders less commonly found associated with nephrocalcinosis were chronic glomerulonephritis and recurrent "idiopathic" renal lithiasis and "idiopathic" hypercalciuria Five (5 5 per cent) of the collected patients with nephrocalcinosis were otherwise normal to all methods of clinical study In an additional 11 per cent of the collected patients

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indeed any, cases of nephrocalcinosis Such factors as elevation of either the calcium or phosphate content of blood, renal tissue fluids or urine would obviously favor precipitation of calcium according to the physicochemical laws of solubility product Similarly the relative alkalinity of renal tissues or urine favors precipitation of calcium In addition deposition of calcium seems to be a frequent bodily response in tissues which are necrotic, degenerating, or have lost viability It seems justifiable to assume that there is no single common denominator in its pathogenesis, but that nephrocalcinosis may result from a number of dissimilar, even unrelated, physiologic mechanisms

CLINICAL FEATURES

Age, sex and race distribution—Nephrocalcinosis may occur at any age, the youngest of our collected patients was 4 months of age, and the oldest was 78 years old Two thirds of the patients were between 20 and 50 years of age when nephrocalcinosis was recognized Significant correlation exists between the age of the patient when nephrocalcinosis is recognized and the nature of the primary causative disorder Elderly patients with nephrocalcinosis are likely to have primary hyperparathyroidism whereas children with nephrocalcinosis almost exclusively have hyperchloremic acidosis There is no correlation in the present series between occurrence of nephrocalcinosis and sex of the patient, and there seems to be no familial or racial predisposition or immunity

Clinical history and physical examination—Clinically nephrocalcinosis is most commonly somewhat of a surprise, appearing on the roentgenogram without having been suspected We could identify no signs or symptoms which should lead the physician to consider nephrocalcinosis

Similarly physical examination of patients with nephrocalcinosis reveals no specific abnormalities Fully half the collected patients were entirely normal to physical examination

Laboratory studies—Inasmuch as nephrocalcinosis is a roentgenographic diagnosis, other clinical laboratory procedures are not necessary to make the diagnosis However laboratory procedures are necessary for the demonstration and identification of the associated causative disorder responsible for the nephrocalcinosis The important procedures in determining the nature of the causative disorder associated with nephrocalcinosis consist of determinations of the concentration of five chemical constituents of blood, namely calcium, phosphorus, chlorides, carbon dioxide combining power, and urea or nonprotein nitrogen These laboratory determinations should be considered the minimal essential tests necessary for evaluation of a patient with nephrocalcinosis Auxiliary determinations which, although not usually altered in patients with nephrocalcinosis, in certain instances may be indicated include alkaline phosphatase, serum protein, and potassium concentrations Other special laboratory studies occasionally helpful in the study of a patient with nephrocalcinosis include culture and microscopic examination of ureteral specimens of urine and tests of renal function Excretion studies of calcium and phosphorus with the patient on a diet containing known quantities of calcium also may be helpful

PATHOLOGIC FINDINGS

Gross and microscopic examination of kidneys removed at necropsy in cases in which nephrocalcinosis had been demonstrated roentgenographically has been infrequently reported; only 13 such cases were gleaned from the medical literature. Seven additional cases were found in the records of the Mayo Clinic, making 20 cases available for our review.

Cause of death.—Study of causes of death of these 20 patients with nephrocalcinosis showed that 13 died in uremia. This indicates the predominant role of renal insufficiency in the death of nephrocalcinotic patients. The only other common contributing cause of death was bronchopneumonia, found in 10 cases.

Renal pathologic findings.—Gross findings in the nephrocalcinotic kidney include a finely granular surface with superimposed scars and cysts, gritty sensation on cutting the kidney, and visible deposits of calcium, especially prominent in the medullary pyramids. In advanced cases extensive medullary destruction can occur (fig. 3). Histologic characteristics of these nephrocalcinotic kidneys (fig. 4) include calcium deposits located chiefly in the walls of collecting tubules and in the medullary interstitial tissue, areas of interstitial fibrosis and round cell infiltration, and large areas in which the tubules have been destroyed or are deformed, with cystic dilation being a common finding. The earliest site of calcium deposition (fig. 5) seems to be the basement membrane of the collecting tubules, and as the deposit of calcium enlarges it deforms, obstructs and destroys the tubule or expands into the peritubular interstitial tissue.

We would like to emphasize our present belief that none of these gross or histopathologic findings can be considered pathognomonic of nephrocalcinosis unless the calcification is also demonstrable roentgenographically. Thus, the

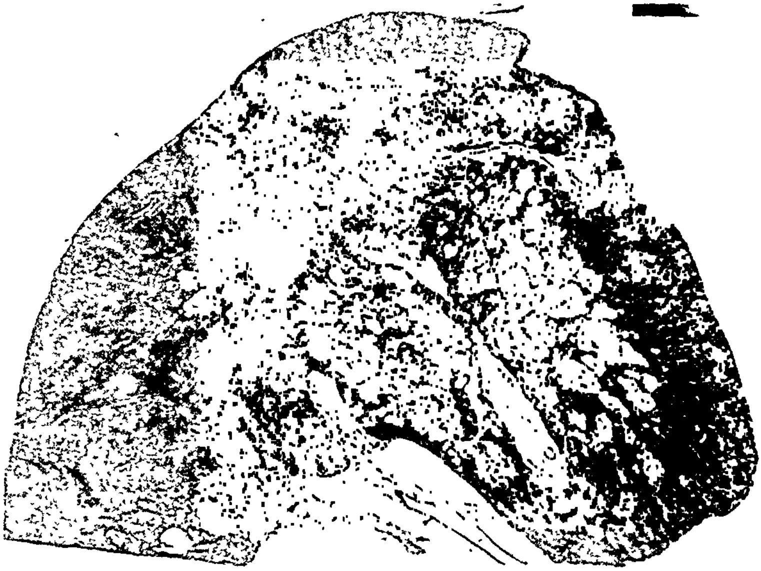

FIG. 3. Extensive destruction of medullary tissue in advanced nephrocalcinosis (hematoxylin and eosin, ×1½).

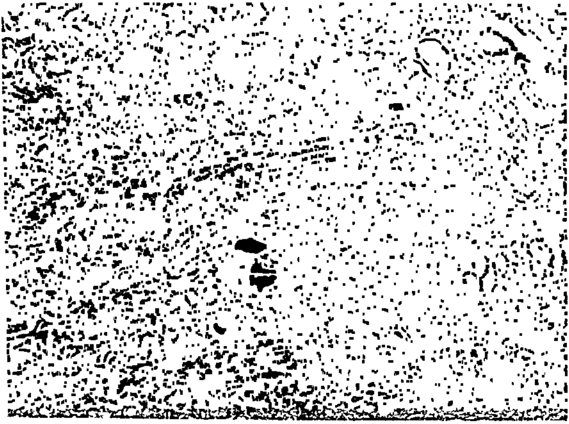

FIG. 4. The characteristic histopathologic findings in the kidney with nephrocalcinosis; deposits of calcium, interstitial infiltration with round cells, interstitial fibrosis, destruction and deformity of collecting tubules may be noted (hematoxylin and eosin, ×30).

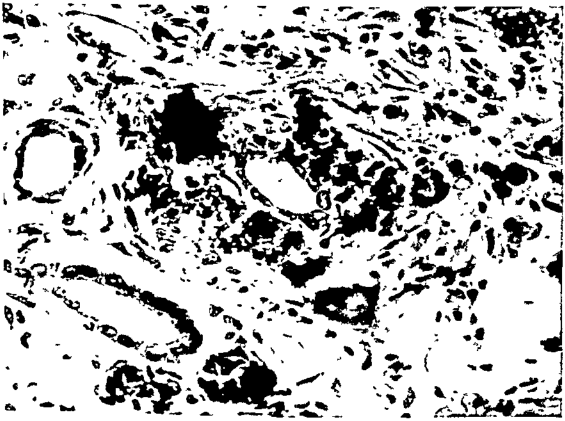

FIG. 5 The primary site of deposition of calcium of nephrocalcinosis in the kidney. Calcification is evident in peritubular interstitial tissue and basement membrane of tubules in the renal medulla (hematoxylin and eosin, ×400).

gross and histologic findings observed in the kidneys in cases of nephrocalcinosis do not seem to be distinguishable pathologically from those which occur in the kidneys of patients with such conditions as long-standing obstructive duodenal ulcer, extensive osteolysis, or even incidentally occurring renal calcification, none of which is demonstrable roentgenographically.

TREATMENT

Nephrocalcinosis, being for the most part a secondary lesion, is logically and properly treated by eradication or control of its primary causative disorder. It is indeed fortunate that such effective and relatively simple therapeutic measures are available to control the primary disorders associated with nephrocalcinosis in most patients. Thus, for a patient with primary hyperparathyroidism and nephrocalcinosis, surgical removal of a hyperfunctioning parathyroid adenoma is essential. For a patient with nephrocalcinosis secondary to hyperchloremic acidosis adequate maintenance therapy with alkali given orally as recommended by Albright and associates is necessary for the control of the physiologic disorder. In cases in which infection is thought to be the primary etiologic factor correction of any mechanical defects, especially obstruction, coupled with administration of appropriate antibiotics is indicated.

RESULTS OF SPECIFIC THERAPY OF CAUSATIVE DISORDER

We have collected data on 26 patients with nephrocalcinosis due to hyperparathyroidism who were followed one or more years after surgical treatment for hyperparathyroidism. In 80 per cent of these cases the roentgenographic appearance of the nephrocalcinosis remained essentially the same, in about 10 per cent the calcification increased and in about 10 per cent it decreased. Renal function remained unchanged in about 25 per cent of the patients, improved in about 35 per cent, and continued to fail in 40 per cent of the patients studied. A similar study of patients with nephrocalcinosis associated with hyperchloremic acidosis followed for one or more years after adequate treatment with alkali was begun, demonstrated that roentgenographic degree of calcification and the renal function of practically all patients so managed either remained the same or improved.

While specific treatment of the primary causative disorder thus appears to be definitely beneficial to the patient with nephrocalcinosis, symptomatic measures aimed at relieving certain of the manifestations of the disorder seem to be of little value. Such measures as restriction of dietary intake of calcium, attempts to change pH of urine, and administration of various vitamins or abstinence from others, have been advocated in certain cases but there is no evidence that benefit resulted unless the causative disorder was also controlled. Administration of hyaluronidase has been suggested in order to alter the colloid equilibrium of urine in such a manner that deposition of calcium in kidneys is prevented, but no proof of its efficacy in the treatment of nephrocalcinosis has been presented as yet.

COURSE AND PROGNOSIS

From consideration of the roentgenographic appearance of nephrocalcinosis, in which a diffuse and rather extensive destructive or degenerative lesion is represented on the roentgenogram, one might expect renal function to be impaired and the prognosis to be poor. However, generalization is difficult and a number of patients with extensive roentgenographic manifestations of nephrocalcinosis have been followed for ten or more years and have maintained normal renal function It thus becomes important to recognize factors which at the time the lesion is first recognized indicate the subsequent course the patient is likely to follow

Analysis of our collected cases of nephrocalcinosis has yielded rather sketchy data relative to the course and prognosis, but the following concepts appear to be justified at this time

1) Roentgenographic evidence of type, extent, or degree of renal calcium deposition is not a reliable indication of the degree of impairment of renal function, hence is not a satisfactory guide to prognosis

2) Prognosis is significantly poorer for patients who have advanced renal insufficiency at the time nephrocalcinosis is recognized However, prognosis is not always dependent on the status of renal function, since the renal function of many patients with moderate degrees of azotemia at the time that nephrocalcinosis is recognized subsequently improves and they live as long as do patients who originally had normal renal function

3) The most important factor in determining the prognosis of a patient with nephrocalcinosis is the nature of its associated causative disorder Early recognition and prompt appropriate treatment of the associated causative disorder appear to offer the patient with nephrocalcinosis the best chance for regaining his health and postponing or avoiding completely the development of fatal uremia

SUMMARY AND CONCLUSIONS

Considering as nephrocalcinosis only that diffuse renal parenchymal calcification which is demonstrable roentgenographically, we have collected from the medical literature 48 cases and from the files of the Mayo Clinic 43 cases of this disorder Analysis of data derived from study of these 91 collected cases of nephrocalcinosis has led us to make the following observations concerning this lesion

The underlying primary disorder responsible for the development of nephrocalcinosis is recognizable clinically in approximately 84 per cent of the cases Three disorders, namely, primary hyperparathyroidism, hyperchloremic acidosis and chronic pyelonephritis, are responsible for 75 per cent of the cases of nephrocalcinosis Less common etiologic disorders are chronic glomerulonephritis, recurrent "idiopathic" renal lithiasis and "idiopathic" hypercalciuria

There are no characteristic symptoms or physical findings attributable to nephrocalcinosis, and its clinical recognition depends on its roentgenographic demonstration

Adequate clinical evaluation of the patient with nephrocalcinosis includes determination of concentration in blood of calcium, phosphorus, carbon dioxide combining power, chlorides and urea or nonprotein nitrogen Proper interpretation of the results of these laboratory determinations usually indicates the nature of the primary disorder responsible for the nephrocalcinosis

Pathologic findings in patients with nephrocalcinosis include deposits of calcium primarily in medullary regions in relation to collecting tubules, and chronic inflammatory changes in medullary interstitial tissues Degenerative changes, including large areas of destruction, replacement with calcareous deposits, cystic dilation and deformity of tubules, and cicatrization, are common findings in kidneys with nephrocalcinosis. However, none of these gross or histologic findings are pathognomonic of roentgenographically demonstrable nephrocalcinosis and any or all may be present in kidneys which do not cast roentgenographic shadows which can be interpreted as nephrocalcinosis.

Early recognition and prompt eradication of the primary causative disorder before advanced renal insufficiency has developed appear to offer patients with nephrocalcinosis the best chance for postponing or avoiding fatal uremia.

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DETERMINATION OF FUNCTION OF THE INDIVIDUAL KIDNEY

TOM E. NESBITT

From the Department of Surgery, University of Michigan, Ann Arbor, Mich.

The need for assaying the functional capacity of an individual kidney frequently confronts the clinician. Our current methods are inadequate in many instances and fail to furnish the desired information. When faced with the differential appraisal of a single kidney one is limited to the visual crudeness afforded by the excretion of various radio opaque iodine compounds or the colorimetric estimation of individual PSP excretion.[1] Theoretically these compounds are ideally suited to such studies, but clinically their scope and usefulness are limited in value. The excretory pyelogram is at best an unreliable guide of functional ability and the laboratory problems concerned with determining iodine excretion limit its clinical application. The "split-function" PSP test described by Rowntree and Geraghty in 1910[2] remains as the simplest indicator of an individual kidney's capacity by providing evidence of tubular function primarily. The results as expressed clinically, however, indicate gross changes only and exact estimations of function are not readily obtained from phenol-red.

Improved tests of glomerular and tubular function in recent years have led to increased knowledge of renal physiology and intensified the attempts at conserving renal parenchyma. In studies of renal disease the 24 hour endogenous creatinine clearance test has been established as an accurate and simple means of evaluating total renal function by measuring glomerular filtration rate.[3] Endogenous creatinine appears in the urine only as a result of glomerular filtration[4, 5] although exogenous creatinine is cleared by tubular secretion as well.[6] Sources of exogenous creatinine must be eliminated if the test is performed satisfactorily, Camara and Newburgh advise a 48 hour meat free period prior to the test for this purpose.[3] When this regimen is followed, the endogenous creatinine clearance is almost identical to known inulin clearances values in the same patients, with normal 24-hour clearances ranging from 125 liters to 150 liters

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The writer wishes to express his appreciation to Henry K. Schoch, M.D., assistant professor of medicine, University of Michigan, whose suggestion provided the incentive for this investigation.

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Other distinct features of the creatinine clearance have proven advantageous. The ease of laboratory determination makes it superior to the urea clearance, another measure of glomerular filtration, but more important it is preferable because it is less affected by discrepancies in timing than the 1-hour urea clearance specimens which, if inaccurate, are reflected as a greater percentage of error. The creatinine clearance reliably indicates degrees of deterioration in renal function in the presence of renal disease, while other clinical tests tend to become progressively unreliable as renal impairment advances. This fact assumes heightened significance when it is realized that it is the patient with altered function who commands more interest from a surgical standpoint. The knowledge that varying degrees of glomerular damage are almost universally accompanied by concomitant tubular disease serves as the basis for another important aspect of this test. This creates a situation allowing one to obtain valuable information by inference about tubular function when glomerular disease is present as established by the creatinine clearance. By contrast, if phenol-red excretion is markedly reduced, it can be assumed significant tubular disease is present, but it does not necessarily follow that glomerular disease has also occurred. Similar limitations are characteristic of most other clinical tests of renal function which are capable of recording gross alterations from normal, while the 24 hour endogenous creatinine clearance measures a single specific function in an exacting fashion expressed in well defined analytical terms.

TECHNIQUES

It seemed likely that this test would lend itself well to the acknowledged need for a better method for differential appraisal of renal disease. Patients were chosen with and without known functional aberrations on whom retrograde pyelograms were to be performed. A meat-free diet was maintained for 48 hours before instrumentation and either prior to or following the examination a 24-hour creatinine clearance was collected. This total function analysis served as the control in each instance for comparison to the individual estimations. At the time of examination ureteral catheters were passed and while in place accurately-timed, 30-minute specimens of urine were collected from each kidney. Venous blood samples for serum creatinine determination were drawn during the period of urine collection and the 30-minute creatinine clearance from each kidney was readily calculated. This value was extrapolated to a 24-hour clearance for comparison to the voided total 24-hour clearance and a highly informative picture thereby obtained of the differential function of each kidney.

Several minor factors of importance should be noted. It is impractical to use ureteral catheters smaller than 6F if dependably accurate urine volumes are to be obtained. It was also noted that unsatisfactory urine collections were more prone to result if the tip of the catheter was not lying at or within the renal pelvis. Lastly, it was found expeditious to induce a degree of diuresis for satisfactory urine volumes by forcing oral fluids for 12 hours beforehand but omitting everything by mouth the last 4 hours to allow use of pentothal analgesia if desired for placement of the catheters. If this fails to produce a diuresis, a temporary infusion of 5 per cent glucose intravenously will suffice.

In actuality, for practical purposes the routines for retrograde pyelography are not altered for the test except that an additional 30 minute period is required for collection of the individual urine specimens after which the usual pyelography is performed In order to avoid errors due to incomplete urine collections from a kidney, a 24-hour *endogenous creatinine clearance should* be collected in each instance to serve as a control for checking the accuracy of the totalled individual clearances

RESULTS

Results obtained have been uniformly accurate when basic requirements for collection were met and have been considerably more informative than previously used techniques in the estimation of renal function A brief discussion of certain specific cases will illustrate the value of the test when applied clinically

Case 1 *(table 1) was that of a 16-year old boy being investigated because* of suspected renal rickets Excretory urography disclosed no evidence of a left kidney shadow while the right suggested abnormality in size At the time of cystoscopy no left ureteral orifice was found and the right kidney was shown by retrograde pyelography to have undergone advanced hydronephrotic atrophy The calculated 24 hour *clearance from the right kidney alone* was 7 4 liters This was essentially identical to the voided 24 hour collection showing 7 6 liters clearance These closely correlated results established without much doubt that the child had but one kidney which had suffered severe functional damage and was not amenable to surgery

Case 2 (table 2) was that of a 44 year *old woman* who had been followed elsewhere for 3 years because of a large calculus in the left renal pelvis She was complaining of persistent left flank discomfort and recurrent urinary tract infections A question was raised regarding left nephrectomy in view of the possible secondary damage already sustained by this kidney which might have relegated *it to a semi nonfunctioning* organ Total 24-hour clearance was 128 liters, calculated clearance from this left kidney alone was 67 liters every 24

TABLE 1 *Case I White man aged 16, renal rickets*

	SPLIT CLEARANCES	24 HOUR CREATININE CLEARANCE
Right kidney	7 4 L	
Left kidney	0	
	7 4 L	7 6 L

TABLE 2 *Case 2 Negress aged 44, left renal calculus*

	SPLIT CLEARANCES	24 HOUR CREATININE CLEARANCE
Right kidney	—	
Left kidney	67 L	
	67 L	128 L

TABLE 3. *Case 3. White woman aged 48; left staghorn calculus*

	SPLIT CLEARANCES	24 HOUR CREATINE CLEARANCE
Right kidney	150 L	
Left kidney	2.6 L	
	152 L	143 L

TABLE 4. *Case 4. White man aged 37; malignant hypertension*

	SPLIT CLEARANCES	24-HOUR CREATININE CLEARANCE
Right kidney	26 L	
Left kidney..	23 L	
	49 L	54 L

TABLE 5. *Case 5. White woman aged 18; bilateral cystine calculi*

	SPLIT CLEARANCES	24-HOUR CREATININE CLEARANCE
Right kidney	57.5 L	
Left kidney	5.9 L	
	63 L	58 L

hours. This demonstrated beyond doubt that from a functional viewpoint, one would not be justified in removing the left kidney. Accordingly, a pyelolithotomy was performed and the patient has made an uneventful recovery.

Case 3 (table 3) was a 48-year-old obese woman with a left staghorn calculus and associated left flank symptoms. Again the question imposed was one of nephrectomy versus pyelolithotomy. Studies indicated a normal 24-hour clearance. The individual clearance was 2.6 liters from the left kidney as compared to 150 liters from the right, as calculated from the 30-minute collections. This clearly indicated the procedure of choice.

Case 4 (table 4) was a 37-year-old lawyer with malignant hypertension. Excretory urograms were unsatisfactory but suggested a left kidney outline. Excretory nephrography, as advocated by Wall and Rose[7] outlined the left kidney well and the pelvis and calyceal system appeared normal. No right kidney was seen. It was felt that the patient had a hypoplastic right kidney—a unilateral ischemic kidney—as the probable explanation for the hypertension. Retrograde studies, however, disclosed a right ectopic pelvic kidney. Nevertheless, due to lack of visualization by nephrography it was believed to be a diseased kidney and a candidate for removal. Clearance studies revealed a total of 54 liters every 24 hours with a clearance from the ectopic kidney of 26 liters and of

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[7] Wall, B and Rose, D K. The clinical intravenous nephrogram. J. Urol., **66**: 304, 1951.

23 liters from the left This pelvic kidney was performing its share of the total work and was no more abnormal than the apparently normal left kidney The man did not come to nephrectomy

Another illustration is case 5 (table 5), an 18 year old girl with bilateral cystine staghorn calculi and severe pain on the left side The studies indicated a total clearance of 58 liters every 24 hours Individual clearance rates were 5 9 liters from the left and 57 5 liters from the right Clearly, then, her total functioning capacity was somewhat less that 50 per cent of normal and the decision was made to conserve the maximum renal parenchyma Because of the symptoms on the left side, a left pyelolithotomy was performed To date she has done very well, but had not such studies been performed, the left kidney might have been sacrificed and the patient's outlook further jeopardized

These cases demonstrate the application of the test in patients with known or suspected renal disease which was inadequately evaluated with other available techniques In this manner the "split creatinine clearance" offers distinct advantages where detailed knowledge is preferable and can be utilized as an adjunct to other diagnostic aids

DISCUSSION

The objective has been the development of a more accurate and informative method of establishing the true functional ability of a single kidney This has been accomplished by application of a reliable clinical test of total renal function, the 24 hour endogenous creatinine clearance All requirements for clinical usage are met as the test is executed easily and the necessary laboratory determinations are simpler to perform than a urea clearance Most important, its worth has proven accurate and valuable when applied to clinical problems This examination is not recommended as a routine procedure, however, as the long established PSP test serves well for the great majority of cases where normal function is assumed It is for the patient with known or suspected renal disease, where sparing functional tissue becomes paramount for preservation of life, that the utilization of this technique is advocated

CONCLUSIONS

The endogenous creatinine clearance determination has been utilized clinically as a "split function" test to estimate individual renal function

The test is simple to perform, reliably accurate, and readily determined by the laboratory

Data are presented to illustrate its application in urologic patients.

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NONOBSTRUCTIVE DILATATION OF THE UPPER URINARY TRACT

JOHN A. HUTCH

In this essay an effort is made to explain that type of hydro-ureter and hydronephrosis which seems to begin at the ureterovesical junction and is not associated with any lesion which actually occludes the lumen of the ureter. The term nonobstructive dilatation of the upper urinary tract was chosen as a title but this term is not accurate as there must be an obstruction at the ureterovesical junction in spite of the fact that large ureteral catheters pass the obstructed area without difficulty.

It is emphasized that any disease or injury which produced trabeculation and sacculization of the bladder (injury or lesion of the spinal cord: obstruction at or below the bladder neck) may be complicated by nonobstructive dilatation of the upper urinary tract.

It is postulated that these changes in the bladder wall (trabeculation and sacculation) are the actual etiologic agent of this dilatation of the upper urinary tract.

It is suggested that our therapeutic efforts should be directed against those factors which cause the bladder trabeculation.

ANATOMY OF URETEROVESICAL JUNCTION

A study of the anatomy of the intravesical ureter is important for an understanding of its part in dilatation of the upper urinary tract.

Figure 1 is a schematic drawing of this structure.

Note that on the mucosal side of the bladder the ureter is securely anchored to the trigone. On the adventitial side the ureter is fixed to the bladder wall by Waldeyer's ureteral sheath which fuses the adventitia of the ureter to the detrusor fibers of the bladder wall. Also note the firm support given the intravesical ureter by the detrusor fibers which lie under it. These three anatomical features assure the oblique passage of the ureter through the bladder wall and serve as a strong support to the intravesical ureter.

From a histological point of view the extravesical ureter consists of three layers, two longitudinal and one circular. In contrast, the intravesical ureter has no circular layer and consists of only longitudinal muscle fibers. Its activity is thus limited to shortening and lengthening. This point assumes importance in the physiology of the ureter.

PHYSIOLOGY

Recently the activity of the intravesical ureter was studied cystoscopically in patients with normal bladders. In all cases indigo carmine had been injected intravenously. During the resting stage the ureteral orifice appeared as a longitudinal slit at the junction of the lateral border of the trigone and the intravesical ureter. During that period in which indigo carmine was spurting from the ureteral orifice no evidence of muscular activity could be observed in either the bladder

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wall of the intravesical ureter However, at the very conclusion of the spurt of blue dye the intravesical ureter and the lateral border of the trigone would rise sharply, carrying the ureteral orifice upward with it At the heighth of this upward excursion the spurt of blue would suddenly stop as though a door had been slapped shut in its path The intravesical ureter and lateral border of the trigone would slowly sink to its resting position to await the next spurt of urine

These observations suggest two conclusions regarding the physiology of the intravesical ureter

1) The intravesical ureter plays no active part in the propulsion of urine from the ureter into the bladder Its role in this function is a passive one like the nozzle of a hose

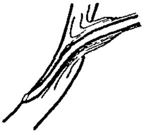


FIG 1

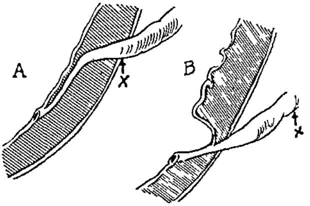


FIG 2

FIG 1 Schematic representation of Waldeyer's ureteral sheath According to Cunningham in his *Textbook of Anatomy*, this sheath consists of longitudinal muscle fibers embedded in fibrocollagenous tissue These muscle fibers are closely applied to adventitia of ureter Proximally they arise from adventitia of ureter about centimeter or so above point at which ureter enters bladder Distally they fuse with bladder musculature Diagram illustrates how carefully anatomy of ureterovesical junction has been planned Ureteral orifice is fixed in mucosal side of bladder by insertion of ureter into trigone Point at which ureter enters b [illegible] lature by media o [illegible] detrusor muscle fi [illegible]

FIG 2 Illustration of normal ureterovesical junction and ureterovesical junction involved in a saccule Point X is point at which ureter enters bladder under normal conditions In abnormal ureterovesical junction illustrated in *B*, X has assumed position well outside bladder

2) The intravesical ureter does play an active part in the prevention of reflux At the conclusion of the spurt of urine the longitudinal muscles of the ureter contract actively and occlude the lumen of the ureter so that no bladder urine may enter

PATHOLOGY OF URETEROVESICAL JUNCTION

Actual pathologic changes at the ureterovesical *junction with the exception* of obstructive lesions like tumor, calculi, infection or ureterocele, confine themselves to varying degrees of weakness of the detrusor muscle which normally lies underneath the intravesical ureter All gradations from the normal (fig 2, *A*) to the mature saccule about the intravesical ureter (fig 2, *B*) can be observed in patients who have bladder trabeculation

Let us go back to figure 2, *A* and mark an X at the point at which the ureter enters the outside of the bladder Now assume that the muscle behind the ureter becomes weakened and forms a saccule, and that the ureter itself is carried into

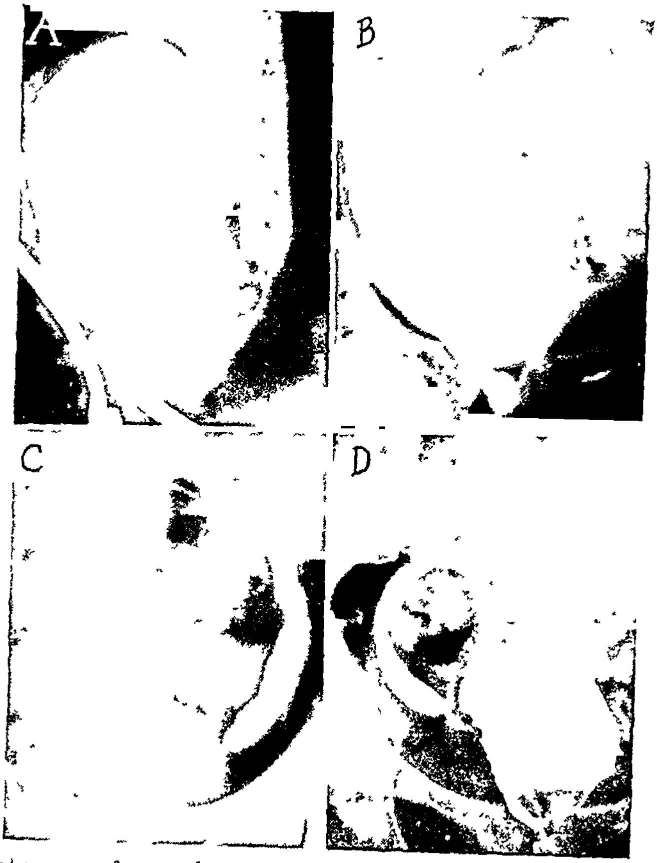


FIG. 3. *A*, cystogram of paraplegic who died of progressive renal failure. At autopsy urinary tract removed intact and cystogram made. X-ray reproduced was fortunate shot which outlines saccule above ureteral orifice and intravesical ureter beautifully. Intravesical ureter can be seen passing along floor of saccule. It is suggested in text that undilated portion of ureter is normal intravesical ureter which has assumed an extravesical position. It is also suggested that point at which ureter begins to dilate is junction of intra- and extravesical ureter.

B, 60-minute delayed cystogram of child with myelomeningocele. In complete x-ray peristaltic wave is apparently passing down ureter forcing Skiodan into lower ureter. Note how undilated intravesical ureter is buckled as fluid is forced into it from above. Had flow of fluid been reversed (i.e. passing from bladder into ureter) at time x-ray was taken, intravesical ureter might have been straight.

C, cystogram in case of cord injury showing extreme bladder trabeculation, bilateral outpocketing of bladder in region of ureterovesical junction and bilateral reflux. Intravesical ureter on left is clearly visible lying in extravesical position. Complete x-ray is reproduced in figure 6.

D, cystogram in case of cord injury illustrating intravesical ureter in extravesical position.

the depth of this diverticulum, so that its course now runs along the floor of this saccule (fig. 2, *B*). The point corresponding to X would now lie outside the outer wall of the bladder. We have, therefore, grounds of a theoretical nature upon which to postulate that under certain conditions in which the intravesical ureter is engulfed in a saccule, the intravesical ureter may assume an extravesical position!

In an earlier paper attention was called to a phenomenon which was observed in 60 per cent of the cystograms of 94 cord injury patients with vesico-ureteral reflux It has been called the "notch sign" or "ureteral gap" and is characterized by a short segment of ureter just before it enters the bladder which does not fill with contrast medium Subsequently, I have been able to secure four cystograms in which this ureteral gap has been filled (fig 3) They confirm the theoretical conclusion that the intravesical ureter may assume an extravesical position They also suggest that the dilatation of the ureter begins at the junction of the intra- and extravesical ureter and therefore does not involve the intravesical ureter or the ureteral orifice

This material suggests two things 1) that the intravesical ureter may assume an extravesical position, and 2) that the dilatation of these ureters begins at the junction of the intravesical and extravesical ureter

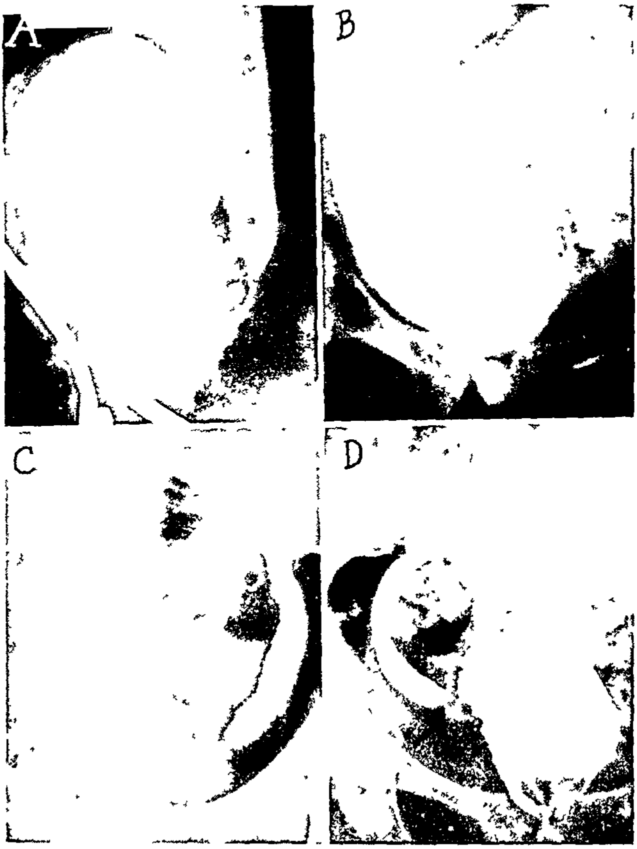
DISCUSSION OF THE MANNER IN WHICH THESE CHANGES AT THE URETERO VESICAL JUNCTION AFFECT THE UPPER URINARY TRACT

Under normal conditions the ureterovesical junction prevents reflux and augments, or at least does not hinder, the passage of urine from the ureter to the bladder When damaged it may lose one or both of these functions

An intravesical ureter which has lost the support of the detrusor fibers which normally lie underneath it will be unable to prevent reflux because there is no longer any firm bladder muscle for it to be compressed against As the intravesical pressure increases bladder urine will leak back up such a ureter and stimulate contraction of the muscles of the ureter Over a period of time such a ureter will dilate from muscular fatigue This chain of events undoubtedly plays a role in the dilatation of the upper urinary tract in those cases where reflux exists There are, however, many cases of hydro ureter and hydronephrosis in which there is no demonstrable reflux Also, many cord injury patients develop dilated upper urinary tracts despite the fact that they have open bladder drainage (suprapubic or urethral) from the day of their injury Certainly reflux could not be a major factor in the dilatation of the upper urinary tract in a patient whose bladder is never allowed to fill Reflux alone does not satisfactorily explain all of these cases Other factors must be sought

For many years urologists have believed that these ureters were obstructed at or near their junction with the bladder Operations have been devised to enlarge this area of the ureter in an effort to enlarge this obstructing segment Others have explored these ureters surgically in an effort to find obstructing valves and bands Still others have divided the ureter above the area of stricture and re implanted the ureter into a new site in the bladder The ureterograms of these patients are characteristic for obstruction or partial obstruction The delayed emptying pyelo ureterograms are convincing evidence for the presence of obstruction at the ureterovesical junction (fig 4) In spite of this apparent obstruction, large ureteral catheters will pass the strictured area without difficulty This obstruction must be one of function and not an actual occlusion of the ureteral lumen[1]

The exact mechanism by which the changes described at the ureterovesical junction produce an obstruction to the flow of urine from the ureter to the blad-



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We have been taught that the hydroureter and hydronephrosis in cases of obstruction at or below the bladder neck are due to back pressure, the increased intravesical pressure being transmitted to the upper urinary tract in some manner More specifically, it may be that the bladder trabeculation damages the ureterovesical junction to such an extent that it either allows reflux to occur or creates an obstruction in the ureter in the manner described on the preceding pages

Bladder trabeculation in patients with injuries to the spinal cord is due to the powerful and erratic impulses which reach the bladder from the damaged distal stump of the spinal cord Bladder spasms powerful enough to force voiding around a large catheter are common in these patients Boyce has measured the electromotive force of these spasms by means of bladder electromyography He found that in patients with hyperactive neurogenic bladders, during a typical bladder spasm "the phases were of enormous electromotive force," as much as 25 times greater than in the normal bladder When a spastic trabeculated neurogenic bladder is freed from its connection with the central nervous system by means of rhizotomy or spinal anesthesia it will assume a normal contour and capacity (fig 6) These points and others indicate quite clearly that the neurogenic bladder becomes trabeculated because of impulses reaching it from the damaged spinal cord

DILATATION OF THE UPPER URINARY TRACT IN CHILDREN

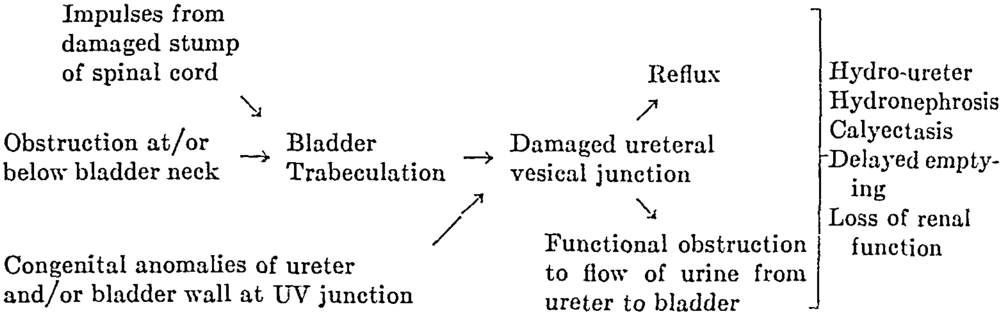
The problem of nonobstructive dilatation of the upper urinary tract in children is a difficult one indeed No single explanation will cover all of these cases The child with congenital bladder neck obstruction develops bladder trabeculation and dilatation of the upper urinary tract in the same manner as an adult with prostatic hypertrophy Likewise the child with meningomyelocele develops bladder trabeculation and dilatation of the urinary tract essentially like the patient with a spinal cord injury There is, however, a third group of patients who have dilatation of their ureters and renal pelves in spite of the fact that they have no bladder trabeculation, and that the ureteral orifice appears normal cystoscopically

Seven patients who would fall into this third group were studied recently at the University of Iowa, and in four of these cases there were associated congenital anomalies of the ureter such as double ureter or septal defects in the bladder wall involving the intravesical ureter When one considers the careful anatomy of the intravesical ureter it seems natural that developmental defects in its structure would be observed occasionally This defect may involve Waldeyer's sheath or the detrusor muscles underneath the intravesical ureter It seems likely that in the paper thin bladder of megalobladder the detrusor fibers are too thin to support the intravesical ureter in its oblique course through the bladder wall As our knowledge of the acquired lesions which produce dilatation of the upper urinary tract increases we will be better able to understand the congenital defects

PATHOGENESIS

Figure 5 portrays the ideas expressed in this paper regarding the pathogenesis of nonobstructive dilatation of the upper urinary tract more concisely than any word picture. It has been pointed out that any pathological condition which produces bladder trabeculation may cause hydro-ureter, hydronephrosis and calyectasis. It has also been shown that impulses from the damaged distal stump of cord injury patients and obstruction to the flow of urine at or below the bladder neck may cause this bladder trabeculation.

FIG. 5. Pathogenesis of nonobstructive dilatation of upper urinary tract


Impulses from damaged stump of spinal cord
Obstruction at/or below bladder neck
Bladder Trabeculation
Congenital anomalies of ureter and/or bladder wall at UV junction
Reflux
Damaged ureteral vesical junction
Functional obstruction to flow of urine from ureter to bladder
Hydro-ureter
Hydronephrosis
Calyectasis
Delayed emptying
Loss of renal function

Bladder trabeculation and sacculization may cause a weakness in the bladder muscle which normally lies under the intravesical ureter. This damages the ureterovesical junction and may even cause it to assume an extravesical position. On a congenital basis some children are born with anomalies which damage the ureterovesical junction. Such an anomaly may involve the ureter as it enters *the bladder or it may involve the bladder wall in such a manner that it cannot* give the intravesical ureter the support it needs to function effectively.

The ureterovesical junction has two functions: one is to prevent reflux; the second is to aid the ureter in propelling urine from the ureter into the bladder. It follows that damage to such a structure would result in a failure of one or both of these functions and result in either reflux or a functional obstruction to the downward flow of urine or both.

It is suggested that as a result of such an obstruction the upper urinary tract begins to dilate at the point of junction of the intravesical and extravesical ureter and progresses to involve the entire upper urinary tract. Reflux per se can cause dilatation of the ureter and renal pelvis by increasing the work load of these structures as they try to expel the regurgitating urine. In many cases these two factors (reflux and functional obstruction) work together to damage the upper urinary tract.

TREATMENT OF NONOBSTRUCTIVE DILATATION OF THE UPPER URINARY TRACT

Therapy must be directed against the bladder trabeculation in those conditions in which bladder trabeculation is the basic etiological factor. In cases of prostatic hypertrophy or bladder neck contraction or urethral stricture, the standard treatment has been the removal of the obstruction and this has relieved the bladder trabeculation with resulting improvement in the upper urinary tract.

On the other hand, our treatment of dilatation of the upper urinary tract in patients with spinal cord disease or injury has been far from satisfactory Since the bladder trabeculation in these cases is due to impulses from the spinal cord, the treatment must be directed toward the de innervation of the bladder Rhizotomy to include the sacral cord at least must be considered Rhizotomies have been performed on cord injury patients for other purposes with marked improve-

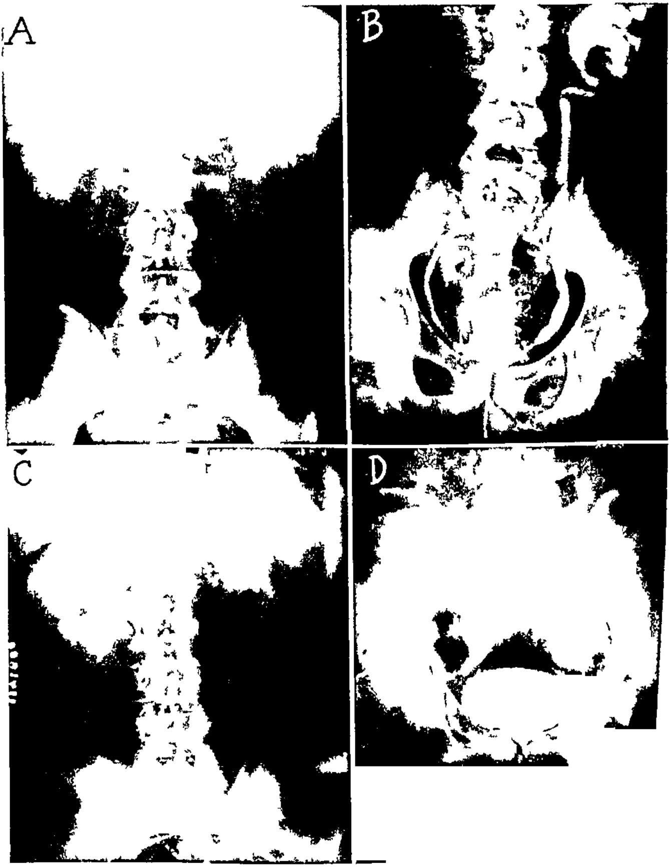


FIG 6 *A*, 15 minute excretory urogram (pre rhizotomy) revealing no excretion of Skiodan in 15 minutes *B* cystogram (pre rhizotomy) revealing severe bladder trabeculation and bilateral reflux *C*, 15 minute excretory urogram (post rhizotomy) revealing much improved function *D*, cystogram (post rhizotomy) Consider changes that have occurred in bladder musculature to explain change in bladder contour

view of the fact that in 25 out of 113 cases of retroperitoneal lipomatous tumors collected by Krogius,[5] the kidney on the affected side was removed at the time of operation.

DIAGNOSTIC UROGRAPHIC FEATURES

A major differential diagnostic point between the urographic findings associated with intrarenal and extrarenal tumors is their effect on the position of the kidney. Ordinarily an intrarenal tumor fails to displace the kidney, while an extrarenal tumor almost invariably does. In addition to displacement of the entire kidney, so-called renal torsion is of considerable diagnostic significance. Weyrauch[6] has described this torsion as being about a vertical, horizontal or transverse axis. Lateral, as well as anteroposterior, exposures are of course important in the determination of lesser degrees of displacement or torsion. The possibility of ureteral displacement which may occur alone or in association with renal displacement must not be overlooked. Obliteration of the psoas shadow has been observed frequently.

Ureteral compression by large liposarcomas with resultant hydronephrosis has been reported. McLaughlin and Sharpe[7] reported a case of a liposarcoma, weighing 56 pounds (25.4 kg.), which obstructed both ureters and caused fatal azotemia. A lipoma, weighing 4½ pounds (2 kg.) in a child, 3½ years old, caused hydronephrosis. Chown,[8] who reported this case in 1939, stated that the kidney returned to normal after removal of the tumor. Actual distortion of the collecting system of the kidney, although not typical, does occur and must be due to pressure of the expanding tumor when the kidney is impinged against adjacent structures or is held immobile by a short pedicle.

MATERIAL STUDIED

The records of 56 patients who had received surgical treatment for fatty retroperitoneal tumors at the Mayo Clinic during a forty-year period subsequent to 1910, were reviewed. Of these, 31 had undergone urographic investigation. In 5 of the early cases this investigation consisted of a plain roentgenogram of the kidney, ureter and bladder only. Retrograde pyelography was first used in 1918 and intravenous pyelography first applied to cases in this series in 1933. Fifteen of the 17 patients who were seen during the past fifteen years were subjected to careful urographic investigation.

FINDINGS

The plain roentgenograms of the abdomen and pelvis commonly called "K.U.B." contributed nothing toward the diagnosis in the 5 cases.

Excretory urograms, retrograde pyelograms or both were made in 26 cases. Displacement of the kidney without distortion of the collecting system was demonstrated in 13 of these cases. Displacement varied considerably in degree and depended, as would be anticipated, on the relative size and position of the tumor. Displacement was often associated with some degree of torsion of the kidney about one or more of its three axes.

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[5] Krogius, A.: Retroperitoneal "lipomas". (Abstr.) J. A. M. A., **86:** 160, 1926.

[6] Weyrauch, H. M., Jr.: The significance of renal torsion in the diagnosis of retroperitoneal tumors. Use of the lateral pyelogram. J. Urol., **41:** 877–892, 1939.

[7] McLaughlin, C. W., Jr. and Sharpe, J. C.: Malignant fatty tumors of the retroperitoneal region: Report of two cases. Am. J. Surg., **41:** 512–518, 1938.

[8] Chown, Bruce: Extraperitoneal lipoma in a child. Am. J. Dis. Child., **57:** 401–403, 1939.

Distortion of the collecting system, in association with displacement of the kidney occurred in 3 cases. As anticipated it was in this group that difficulty with correct interpretation occurred. Although some degree of ureteral displacement occurred in association with displacement of the kidney in many of the cases, ureteral displacement without displacement of the kidney was found in 3 cases in which small tumors were situated in the retroperitoneal space more caudad than the kidney. In an additional 2 cases, the kidneys were neither displaced nor their collecting systems distorted, but a soft tissue mass contiguous with the kidney but apparently not otherwise associated, could be seen. Negative findings were recorded in 5 cases.

REPORT OF CASES

Four interesting representative cases are included.

Case 1.—A woman, 50 years old, gave as her chief complaint a mass in the left side of the abdomen. As far as she knew it had been present for approximately one year. She mentioned only occasional mild, nondescript abdominal discomfort. She had no significant urinary complaints. Physical examination revealed a large firm mass occupying the left side of the abdomen. Microscopic examination of the urine revealed only an occasional pus cell. The excretory urogram and retrograde pyelogram demonstrated displacement of the left kidney to the right side with torsion of 180 degrees about the vertical axis (fig. 1*a* and *b*). The dis-

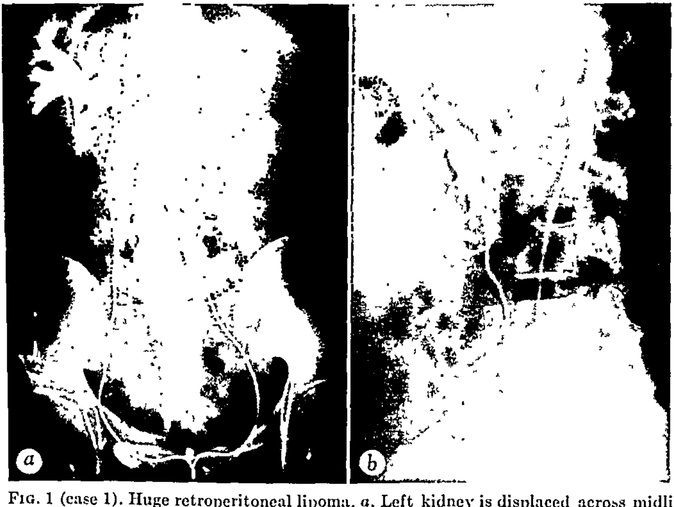

Fig. 1 (case 1). Huge retroperitoneal lipoma. *a*, Left kidney is displaced across midline and rotated 180 degrees about the vertical axis. *b*, Anterior position of kidney is shown in lateral film.

placed kidney returned to its normal position after removal elsewhere of a lipoma weighing 22 pounds (10 kg.).

Case 2.—A woman, 51 years old, had been seen and treated at the clinic several times since she had been given a diagnosis of syphilis of the central nervous system when she was 40 years old. The chief complaint at the time of the admission under consideration herein, was postprandial gaseous distention. She had first noticed this eight months before and it had been progressive in character. She had some associated abdominal discomfort which was relieved by passage of flatus. Her only urinary complaint was nocturia. Microscopic examination of the urine demonstrated only an occasional pus cell. On physical examination a firm, slightly irregular mass could be palpated filling the left side of the abdomen. A retrograde pyelogram showed marked displacement of the left ureter across the midline with displacement of the left kidney to a lesser degree than in case 1 (fig. 2*a*). The tumor, a liposarcoma, weighed 1,600 gm. (fig. 2*b*).

Case 3.—The patient was a man, 67 years old, whose chief complaint was a mass low in the abdomen which he thought had fluctuated in size since he first noticed it ten months before. His only urinary symptoms were those of mild obstruction. Left retrograde pyelogram (fig. 3) demonstrated that the left kidney was low in the left lower quadrant and its pelvis and calyces were distorted into a perfect half-moon. The left flank was explored and a large retroperitoneal liposarcoma was partially removed. The kidney was not invaded by the tumor despite the appearance of the retrograde pyelogram.

Case 4.—The patient, a woman 49 years old, was first examined at the clinic when she was 38 years old. The physical findings were not abnormal at that time. Thirteen months before the current admission, she had noticed a mass in the right lower part of the abdomen. Five months later a pain developed in the right side

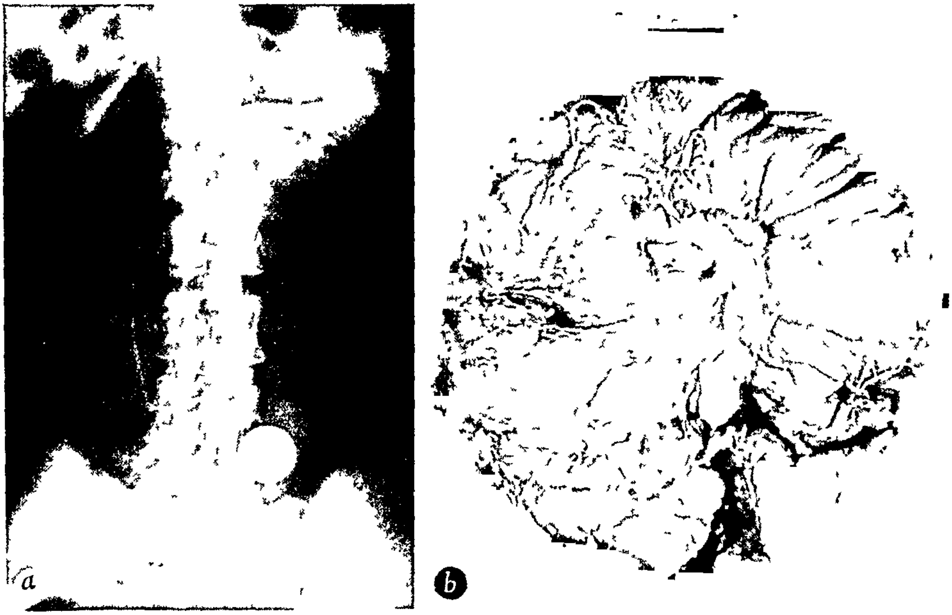

FIG. 2 (case 2). Liposarcoma *a*, Left ureter and lower pole of left kidney are displaced across midline *b*, Specimen removed.

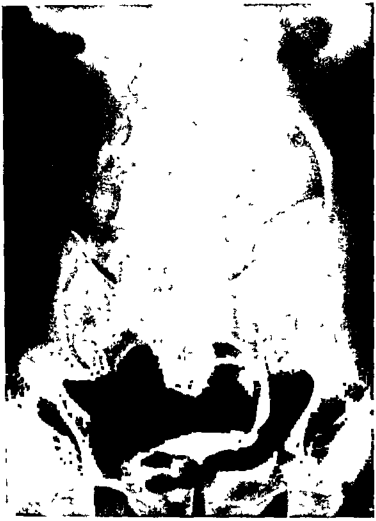

FIG. 3 (case 3). Displacement of left kidney and distortion of its collecting system by liposarcoma which did not invade the kidney.

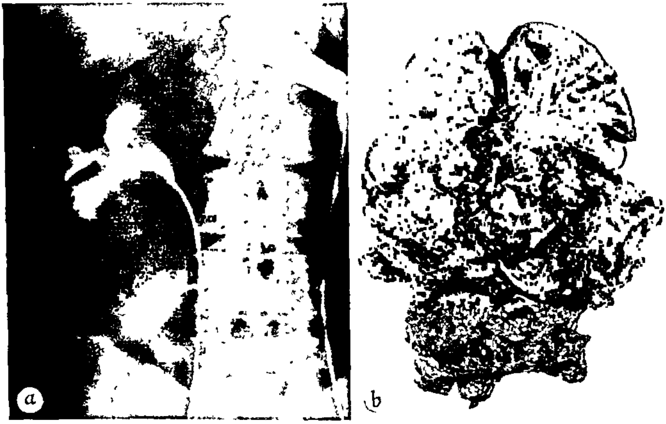

FIG 4 (case 4). *a*, Crescentic deformity involving lower pole of right kidney with deformity of lower calyces. *b*, Invasion of kidney by liposarcoma.

of the abdomen. The abdomen was explored surgically elsewhere and a retroperitoneal mass was described. At the time of examination at the clinic she was having no abdominal or urinary symptoms. Urinalysis gave negative results. Physical findings included description of a mass filling the right side of the abdomen. A retrograde pyelogram (fig. 4*a*) demonstrated a crescentic deformity of the lower pole of the right kidney with distorted lower calyces. The kidney appeared to be displaced anteriorly in the plain lateral roentgenogram. At operation the kidney (fig. 4*b*) was found to be invaded and was removed with the main liposarcomatous mass.

SUMMARY

Thirty-one out of a group of 56 patients with retroperitoneal fatty tumors seen at the Mayo Clinic in forty years had been studied by urographic methods. The significant findings on urographic investigation were displacement of the kidney or ureter or both with associated distortion of the collecting system in isolated cases. A plain roentgenogram of the abdomen alone had no diagnostic value as demonstrated by 5 cases in the series. In 73 per cent of the 26 cases in which an excretory urogram or retrograde pyelogram or both had been made, significant displacement of the kidney or ureter or both was demonstrated on the affected side.

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FURTHER OBSERVATIONS WITH DELAYED CYSTOGRAMS

R. G. BUNGE

From the Department of Urology, University Hospitals, State University of Iowa, Iowa City, Iowa

In a previous article,[1] observations in children using the delayed cystographic x-ray method of Dr. Charles M. Stewart were reported. Stewart first noticed ureteral reflux in a patient whose immediate cystogram was normal. The delayed cystogram occurred as a result of a technician's error.[2] This present report is concerned with observations on a larger series of patients, but includes the previous cases.

METHOD

Delayed cystograms were made by filling the bladder slowly by the catheter to comfort (90–120 ml. in adults, 30–90 ml. in children) with warm 10 per cent skiodan solution. No effort was made to overdistend the bladder. The catheter was withdrawn and an x-ray film was exposed immediately, giving the ordinary cystogram. The patient was told to retain the instilled solution. Ambulation was allowed, and after the elapse of 30 minutes another x-ray picture was taken, and again after 60 minutes had elapsed, following the instillation of skiodan. Excretory urograms were obtained in most of the cases either 24 hours before or after cystography to avoid erroneous interpretation. If the patient was too young to co-operate, the urethral catheter was left indwelling and clamped. Cystoscopic examinations were done in all cases, except normal children and pregnant females.

RESULTS

Twenty-four normal children and adults were examined (table 1). These ranged in age from 9 months to 74 years. In one, an asymptomatic hydronephrosis was found. Ureteral reflux did not appear in any of the examinations.

Thirty-six cases of neurogenic bladder were examined (table 2). Ureteral reflux appeared in 8 cases. In 1 case the reflux was not present on the immediate cystogram, but was apparent on the delayed film. In two cases a rather surprising finding was reflux on the immediate film, but none on subsequent delayed pictures. Patients with bladder residual urine over 450 ml. did not have ureteral reflux. Those with ureteral reflux had residual urines ranging from 30 to 250 ml.

Twenty-eight cases of bladder neck obstruction ranging in age from 20 months to 85 years were examined (table 3). Ureteral reflux was detected mostly in the children's group (6 children, 3 adults). In three pediatric cases, reflux did not appear on the ordinary cystograms but was detected on subsequent delayed films.

Twenty-four cases of full-term pregnant women were examined (table 4). Five had excretory urograms which revealed the typical upper urinary tract dilatation. Ureteral reflux was not detected in any case.

Accepted for publication April 10, 1953.

[1] Bunge, R. G.: J. Urol., 70: 729, 1953.

[2] Stewart, C. M.: Personal communication.

TABLE I. *Normal subjects*

NO.	PATIENT	SEX	AGE IN YEARS	DIAGNOSIS	BLADDER RESIDUAL URINE (cc.)	IVP	CYSTOGRAMS		
							0′	30′	60′
1.	M. T.	F	9 mo.	Normal subject	0	Normal	0	0	0
2.	L. M.	F	4	Normal subject	0	Not taken	0	0	0
3.	A. B.	M	5	Normal subject	0	Normal	0	0	0
4.	E. M.	M	6	Normal subject	0	Not taken	0	0	0
5.	C. C.	M	7	Normal subject	0	Not taken	0	0	0
6.	M. B.	M	7	Normal subject	0	Not taken	0	0	0
7.	R. R.	M	8	Normal subject	0	Normal	0	0	0
8.	T. H.	M	8	Normal subject	0	Not taken	0	0	0
9.	M. S.	M	8	Normal subject	0	Not taken	0	0	0
10.	M. Z.	F	9	Normal subject	0	Normal	0	0	0
11.	J. A.	F	9	Normal subject	0	Normal	0	0	0
12.	C. K.	M	12	Normal subject	0	Not taken	0	0	0
13.	P. C.	M	12	Normal subject	0	Not taken	0	0	0
14.	G. T.	M	13	Normal subject	0	Normal	0	0	0
15.	M. B.	F	14	Normal subject	0	Poor detail	0	0	0
16.	J. B.	M	15	Normal subject	0	Not taken	0	0	0
17.	C. P.	F	18	Normal subject	0	Not taken	0	0	0
18.	N. H.	F	19	Normal subject	0	Lt. hydronephrosis	0	0	0
19.	W. B.	M	19	Normal subject	0	Not taken	0	0	0
20.	Y. Z.	F	24	Normal subject	0	Normal	0	0	0
21.	C. D.	F	31	Normal subject	0	Normal	0	0	0
22.	J. G.	M	31	Normal subject	0	Normal	0	0	0
23.	J. H.	F	40	Normal subject	0	Normal	0	0	0
24.	L. A.	F	74	Normal subject	0	Normal	0	0	0

KEY: 0—No ureteral reflux; L—Left ureteral reflux; R—Right ureteral reflux; Bil—Bilateral ureteral reflux; SP—Suprapubic tube; CR—Complete retention; 0′—Immediate cystogram; 30′—Cystogram at 30 minute interval; 60′—Cystogram at 60 minute interval.

Twenty-three patients with urological disease in whom ureteral reflux would not ordinarily be clinically suspected were examined (table 5). Five adults had ureteral reflux; one was picked up by the delayed technique. Two adult cases with reflux failed to show it under spinal anesthesia. Four children with recurrent urinary infections were shown to have ureteral reflux. In three it was not revealed by the ordinary cystogram.

Seven cases, classified as a miscellaneous group, were examined (table 6). The possibility of ureteral reflux was entertained but not substantiated.

DISCUSSION

Ureteral reflux is rare in normal children[3] and adults,[4] but it is more apt to occur in childhood. This suggests the possibility of maturation of ureteral physiology, since reflux is present normally in lower animals, such as the rabbit.

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[3] Campbell, M. F.: Pediatric Urology, New York: Macmillan Co., 1937, vol. 1, p. 70.
[4] Sampson, J. A., Bull. Johns Hopkins Hosp., 14: 334, 1903.

TABLE 2 *Neurogenic bladders*

NO	PATIENT	SEX	AGE IN YEARS	DIAGNOSIS	BLADDER RESIDUAL URINE (cc)	IVP	CYSTOGRAMS		
							0	30	60
1	P R	M	12	Paraplegic 4 months	20	Poor detail	0	0	0
2	M G	M	17	Paraplegic 3 years	180	Normal	R	R	R
3	P T	M	18	Paraplegic 6 months	?	Normal	R	0	0
4	H B	F	23	Paraplegic 2 years	125	Bil hydronephrosis	0	0	0
5	M W	F	46	Paraplegic ? years	0	Poor detail	0	0	0
6	C S	M	54	Paraplegic 4 years	100	Poor detail	0	0	0
7	E E	F	4	Transverse myelopathy L 1	150	Rt indeterminate, lt normal	0	0	0
8	H C	M	62	Tabes dorsalis	20	Normal	0	0	0
9	B R	M	67	Tabes dorsalis	50	Poor detail	0	0	0
10	R C	F	42	Erb's spastic paralysis	1000	Normal	0	0	0
11	S L	M	3	Meningomyelocele	30	Rt normal, lt hydronephrosis	L	L	L
12	D C	M	3	Meningomyelocele	50	Normal	0	0	0
13	C E	F	4	Meningomyelocele	0	Normal	0	0	0
14	G L	F	8	Meningomyelocele	110	Normal	0	0	0
15	L L	F	8	Meningomyelocele	50	Bil hydronephrosis	0	0	0
16	J H	F	9	Meningomyelocele	250	Bil hydronephrosis	0	Bil	Bil
17 *	M C	F	11	Meningocele	150	Lt hydronephrosis	L	L	L
18	J R	F	12	Meningomyelocele	50	Bil hydronephrosis	Bil	0	0
19	P B	F	15	Meningomyelocele	150	Rt normal lt hydronephrosis	L	L	L
20	D K	M	25	Meningomyelocele	300	Normal	0	0	0
21	W N	M	4	Landry Guillain Barre syndrome	SP	Bil hydronephrosis	0	0	0
22	K H	F	6	Neurogenic bladder ? cause	160	Bil hydronephrosis	Bil	Bil	Bil
23	D D	M	6	Encephalomeningomyelitis	100	Bil hydronephrosis	0	0	0

TABLE 2.—(*Continued*)

NO.	PATIENT	SEX	AGE IN YEARS	DIAGNOSIS	BLADDER RESIDUAL URINE (cc.)	IVP	CYSTOGRAMS		
							0'	30'	60'
24.	R. N.	M	23	Ascending myelitis	SP	Normal	0	0	0
25.	E. F.	F	19	Atonic bladder, ? cause	0	Poor detail	0	0	0
26.	J. K.	F	21	Atonic bladder, ? cause	30	Normal	0	0	0
27.	L. R.	F	54	Atonic bladder, ? cause	500	Normal	0	0	0
28.	M. W.	F	63	Atonic bladder, ? cause	600	Normal	0	0	0
29.	H. H.	M	51	Diabetes mellitus, atonic bladder	20	Normal	0	0	0
30.	M. B.	F	35	Spinal cord tumor	450	Normal	0	0	0
31.	A. F.	M	62	Multiple sclerosis	700	Bil. hydronephrosis	0	0	0
32.	W. W.	F	62	Intrathecal alcohol	500	Normal	0	0	0
33.	L. G.	M	10	Anterior poliomyelitis	150	Normal	0	0	0
34.	D. D.	M	19	Anterior poliomyelitis	50	Bil. hydronephrosis	0	0	0
35.	H. W.	M	39	Anterior poliomyelitis	30	Bil. hydronephrosis	0	0	0
36.	E. S.	M	39	Herniated nucleus pulposus	SP	Normal	0	0	0

* Right nephrectomy for hydronephrosis.

The altered function of neurogenically disturbed bladders raises suspicions of altered ureteral physiology. Ureteral reflux is more apt to be present, and large residual bladder urines are not associated with reflux. This is in agreement with the findings of Bors and Comarr whose work we were not aware of at the time this paper was first written.[5] The detection of bilateral hydronephrosis does not allow prediction that ureteral reflux will be present.

Ureteral reflux is more apt to occur in bladder neck obstruction of childhood, and there is one important point here: in children who have had their obstruction removed and persistently have pyuria, unsuspected delayed ureteral reflux may be the underlying cause. We have successfully attacked this problem by using Hutch's vesicoureteroplasty.[6]

The altered state of the upper urinary tract during pregnancy suggested the possibility of ureteral reflux occurring under the conditions of this investigation (table 4). This was not found to be true; however, it would be highly interesting to employ delayed cystography in a group of "pyelitis of pregnancy" patients.

[5] Bors, E. and Comarr, E.: J. Urol., **68:** 691, 1952.

[6] Hutch, J. A.: J. Urol., **68:** 457, 1952.

TABLE 3 *Bladder neck obstruction*

NO	PATIENT	SEX	AGE IN YEARS	DIAGNOSIS	BLADDER RESIDUAL URINE (cc)	IVP	CYSTOGRAMS		
							0	30	60
1	D N	M	20 mo	Prostatic valves	225	Bil hydronephrosis	0	0	0
2	P P	F	4	Congenital bladder neck obstruction	100	Bil hydronephrosis	0	Bil	Bil
3	J B	M	5	Congenital bladder neck obstruction	0	Normal	0	Bil	Bil
4	W S	M	7	Congenital bladder neck obstruction, postoperative	5	Normal	L	L	Bil
5	G T	M	7	Congenital bladder neck obstruction, postoperative	25	Bil hydronephrosis	0	0	0
6	M M	F	7	Congenital bladder neck obstruction	75	Poor detail	0	L	0
7	J B	F	7	Congenital bladder neck obstruction, postoperative	0	Bil hydronephrosis	Bil	Bil	Bil
8	R S	M	9	Congenital bladder neck obstruction	80	Normal	0	0	0
9	W H	M	10	Congenital bladder neck obstruction	250	Bil hydronephrosis	Bil	Bil	Bil
10	N T	F	47	Bladder neck contracture	450	Normal	0	0	0
11	U C	F	47	Bladder neck contracture	100	Bil hydronephrosis	Bil	Bil	Bil
12	E H	F	57	Bladder neck contracture	SP	Bil hydronephrosis	R	R	R
13	J H	M	58	Bladder neck contracture	100	Bil hydronephrosis	Bil	Bil	Bil
14	A G	F	68	Bladder neck contracture	100	Normal	0	0	0
15	F B	M	73	Bladder neck contracture	60	Normal	0	0	0
16	H P	M	60	Benign prostatic hypertrophy	400	Not taken	0	0	0
17	J M	M	70	Benign prostatic hypertrophy	175	Not taken	0	0	0
18	F O	M	70	Benign prostatic hypertrophy	250	Normal	0	0	0

TABLE 3.—(*Continued*)

NO.	PATIENT	SEX	AGE IN YEARS	DIAGNOSIS	BLADDER RESIDUAL URINE (cc.)	IVP	CYSTOGRAMS 0′	30′	60′
19.	M. P.	M	73	Benign prostatic hypertrophy	400	Not taken	0	0	0
20.	R. B.	M	73	Benign prostatic hypertrophy	CR	Not taken	0	0	0
21.	R. B.	M	73	Benign prostatic hypertrophy	500	Not taken	0	0	0
22.	C. H.	M	75	Benign prostatic hypertrophy	CR	Not taken	0	0	0
23.	F. W.	M	79	Benign prostatic hypertrophy	450	Not taken	0	0	0
24.	W. S.	M	79	Median bar	250	Not taken	0	0	0
25.	E. D.	M	80	Benign prostatic hypertrophy	CR	Not taken	0	0	0
26.	J. E.	M	83	Benign prostatic hypertrophy	CR	Not taken	0	0	0
27.	T. R.	M	84	Carcinoma of the prostate	200	Not taken	0	0	0
28.	H. L.	M	85	Benign prostatic hypertrophy	CR	Normal	0	0	0

TABLE 4. *Pregnancy*

NO.	PATIENT	AGE	TERM	GRAVID	PARA	CYSTOGRAMS 0′	30′	60′	URINE	IVP
1.	N. LaM.	16	Near full	1	0	0	0	0	Negative	Not taken
2.	D. H.	17	Full	1	0	0	0	0	Negative	Rt. hydronephrosis
3.	S. B.	19	Full	2	1	0	0	0	5 wbc/hpf	Not taken
4.	H. S.	19	Full	1	0	0	0	0	Negative	Not taken
5.	V. B.	20	Full	2	1	0	0	0	Negative	Bil. hydronephrosis
6.	P. B.	21	Full	2	1	0	0	0	Negative	Not taken
7.	D. G.	21	Full	4	3	0	0	0	Negative	Rt. hydronephrosis, lt. normal
8.	G. O'C.	22	Full	4	3	0	0	0	Negative	Not taken
9.	M. T.	22	Full	3	2	0	0	0	Negative	Not taken
10.	M. R.	22	Full	1	0	0	0	0	Negative	Not taken
11.	D. L.	23	Full	2	1	0	0	0	Negative	Not taken
12.	D. T.	23	Full	3	2	0	0	0	Negative	Not taken
13.	R. D.	23	Full	2	1	0	0	0	Negative	Rt. hydronephrosis, lt. normal
14.	C. C.	25	Full	2	1	0	0	0	Negative	Bil. hydronephrosis
15.	M. D.	25	Full	2	1	0	0	0	Negative	Not taken
16.	L. P.	25	Full	4	2	0	0	0	10 wbc/hpf	Not taken
17.	V. S.	27	Full	7	6	0	0	0	Negative	Not taken
18.	M. B.	27	Full	4	3	0	0	0	3–5 wbc/hpf	Not taken
19.	M. M.	27	Full	5	4	0	0	0	Negative	Not taken
20.	L. F.	33	Full	7	6	0	0	0	Negative	Not taken
21.	E. G.	33	Full	8	7	0	0	0	Negative	Not taken
22.	G. C.	34	Full	5	4	0	0	0	10 wbc/hpf	Not taken
23.	D. C.	35	Full	9	6	0	0	0	Negative	Not taken
24.	J. K.	39	Full	7	6	0	0	0	6 wbc/hpf	Not taken

TABLE 5 *Urological disease*

NO	PATIENT	SEX	AGE IN YEARS	DIAGNOSIS	BLADDER RESIDUAL URINE (cc)	IVP	CYSTOGRAMS		
							0	30	60
1	O S	M	52	Bladder neck contracture	50	Bil hydronephrosis	0	0	L
	O S			With spinal anesthesia			0	0	0
2	W S	M	67	Trigonal scar gapping ureteral orifices	50	Normal	R	R	R
	W S			With spinal anesthesia			0	0	0
3	M M	F	3	Recurrent urinary tract infection	20	Bil hydronephrosis	0	Bil	L
4	B B	F	5	Unexplained chills, fever	0	Normal	0	R	R
5	M P	F	5	Pyuria	0	Normal	0	0	0
6	M G	F	9	Recurrent urinary tract infection	20	Normal	Bil	0	0
7	P B	F	9	Recurrent urinary tract infection	25	Normal	0	Bil	L
8	J C	F	9	Acute cystitis	0	Normal	0	0	0
9	B C	F	22	Congenital hydronephrosis and hydroureter	20	Bil hydronephrosis	Bil	Bil	Bil
10	C F	M	23	Diabetes and chronic pyelonephritis	0	Poor detail	0	0	0
11	M A	F	27	Left renal stone	0	Not taken	Bil	Bil	0
12	G P	F	29	Bilateral nephrolithiasis	0	Bil hydronephrosis	0	0	0
13	J M	F	31	Recurrent cystitis	0	Normal	0	0	0
14	M D	F	34	Recurrent cystitis	0	Bil hydronephrosis	0	0	0
15	L T	F	33	Scarred left ureteral orifice	0	Normal	0	0	0
16	V J	F	39	Diabetes, cystitis	0	Rt hydronephrosis	0	0	0
17	V J	F	39	Acute cystitis	0	Bil hydronephrosis	0	0	0
18	A S	F	46	Acute cystitis	0	Normal	0	0	0
19	H H	M	51	Bilateral ureterocele, postoperative	0	Bil hydronephrosis	0	0	0
20	L E	F	57	Bladder stones	25	Normal	0	0	0
21	W S	M	67	Three months after resection of bladder tumor near left ureteral orifice	0	Poor detail	L	L	L
22	B G	F	78	Bilateral nephrolithiasis	0	Bil hydronephrosis	0	0	0
23	Q S	F	63	Stress incontinence	0	Normal	0	0	0

not offer the maximum possible cure rate. Can this same superficial carcinoma spread by the vesical lymphatics to the contralateral side of the bladder and from there to the regional lymph nodes? If so, then it would seem that simple segmental resection is probably inadvisable for any such case. If, however, segmental resection is performed for this type case, it would appear that a considerably larger portion of the bladder should be excised than is now commonly practiced. If simple cystectomy or segmental resection is used, it may be that a higher cure rate will be obtained by routine use of lymphadenectomy in each case. These questions remain unanswered. Relative confusion and indecision still reign and can probably be resolved, if only in part, by a clearer understanding of the method of tumor spread within the bladder and extravesically.

The distribution of pelvic and abdominal lymphatics, and lymphatic drainage from specific pelvic and abdominal organs, has been the subject of much excellent work.[6] The lymphatics of the bladder have received scant attention in the medical literature. Powell[7] has illustrated in the stillborn fetus, the fine anatomical network of lymphatics within the bladder. Powell's method ably demonstrates the anatomy of the vesical lymphatic system, but does not portray the functional nature of the system under physiological conditions. It is necessary to correlate the physiological and anatomical aspects of this system prior to stating categorically the nature of the lymphatic drainage. For example, Powell states that there is relatively little anastomosis of the lymph vessels across the anterior median line of the bladder. It is not known whether this situation obtains in the living subject as it does in the postmortem bladder specimen. An experiment has been conducted, therefore, to study vesical lymphatics by a physiological approach.

MATERIAL AND METHODS

Operative procedures were performed on ten healthy, male and female mongrel dogs, using intravenous nembutal anesthesia and observing routine surgical precautions. The large molecule colloidal suspension used for the experiment consisted of an autoclaved solution containing five parts Higgins India ink and one part distilled water. The suspension was injected by means of a tuberculin syringe and a number 26 hypodermic needle.

The bladder was exposed through a low midline or right paramedian incision. The total bladder was arbitrarily divided into ten areas; four anterior, four posterior and two lateral (fig. 1). A small opening was made in the midline of the bladder at a point distant to the area to be injected. One-tenth of a cubic centimeter of the prepared suspension was injected submucosally into one of the ten areas previously described. One dog was used for each injection site. Care was taken to inject the suspension as gently as possible to prevent traumatic dissemination of particles. The injected material appeared as a submucosal bleb

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[6] Parker, A. E.: Studies on the main posterior lymph channels of the abdomen and their connections with the lymphatics of the genito-urinary system. Am. J. Anat., **56**: 409–443, 1935.

[7] Powell, T. O.: Studies in the lymphatics of the female urinary bladder. Surg. Gynec. & Obst., **78**: 605–609, 1944.

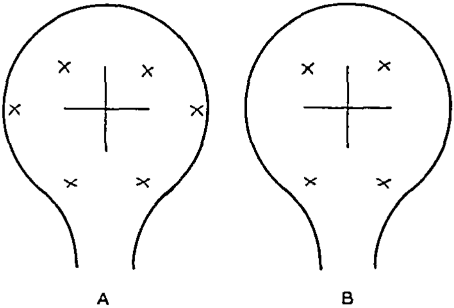

FIG. 1. *A*, diagrammatic representation of anterior bladder wall illustrating four areas on anterior wall and two on lateral walls in which India ink suspension was injected. *B*, diagrammatic representation of posterior bladder wall illustrating four areas injected on posterior wall.

occupying an area of only one to two millimeters in diameter. The bladder and abdominal wall were closed in the usual fashion.

Twenty-four hours later the dog was sacrificed and an immediate autopsy performed. The ureters and vesical neck were ligated and the bladder excised. The bladder was distended with 10 per cent formalin-saline solution and placed in a jar containing a similar solution for fixing. A total pelvic and abdominal evisceration was then performed followed by complete exposure and dissection of pelvic and abdominal lymph node chains (fig. 2). All nodes were sectioned and those grossly involved with India ink particles were noted and their site recorded. The bladder specimen was fixed in the formalin solution for one week and then sectioned in a coronal plane through the site of the injection. This section was mounted in a paraffin block and microsections made and stained with a hemotoxylin-eosin preparation.

RESULTS

Several general observations were noted which were applicable to each of the ten bladder areas injected with the suspension. No particles of India ink were observed in the mucosal layer in any of the sections studied. These particles disseminated predominately within macrophage cells observed in the lymphatic channels accompanying blood vessels in the muscle layers and less frequently in the submucosal and adventitial layers. The adventitia contained particles locally in nine out of ten cases. Most distant spread within the bladder was constantly noted in the muscle layers rather than in the submucosa or adventitia. Twenty-five to fifty per cent of the bladder circumference in the sections studied was invaded with India ink particles. Lymph nodes were involved in six out of the ten dogs.

Anterior Bladder Wall

Left lower quadrant: The suspension had been injected 0.5 cm. to the left of the midline. Microscopic examination revealed particle-filled macrophages trans-

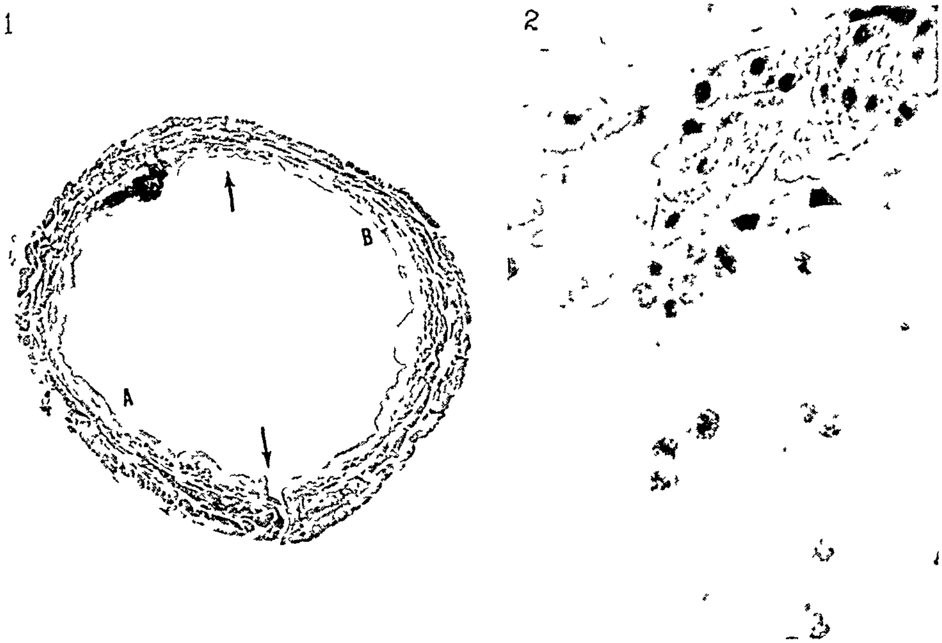

FIG. 4. *1*, Coronal section of bladder demonstrating site of India ink injection in submucosa 1 cm. to right of anterior midline (arrows) Dissemination of particles has occurred in muscle layers to points *A* and *B*. *2*, Photomicrograph of muscle layers taken through point *B* in *1* to demonstrate particles of India ink within macrophages

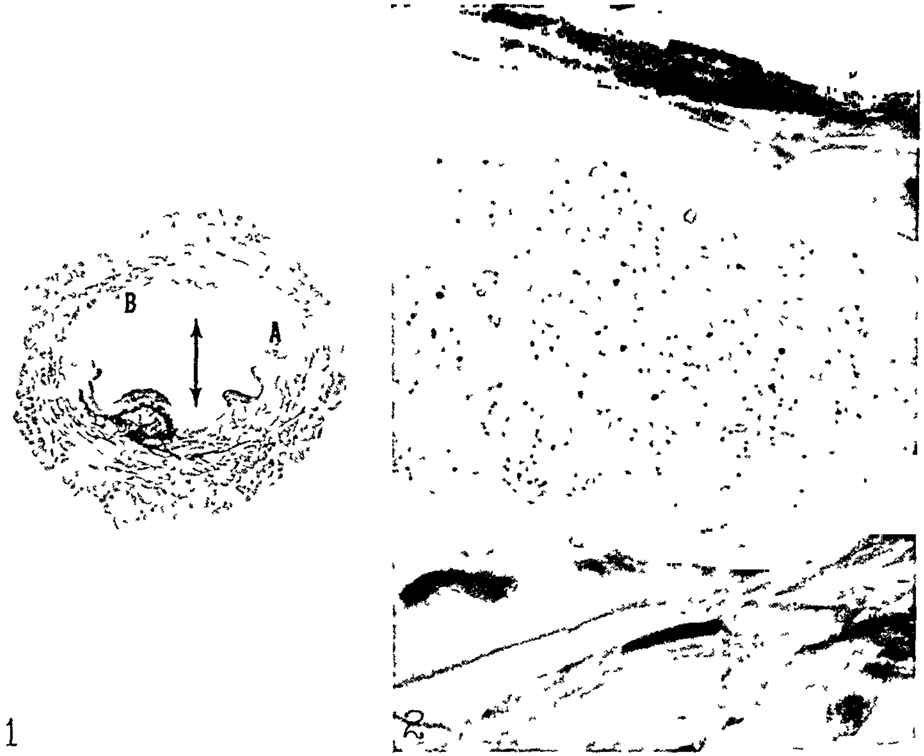

FIG. 5. *1*, Coronal section of bladder illustrating site of India ink injection 0.5 cm to right of midline (arrows). Particles of India ink have disseminated to points *A* and *B*. *2*, Photomicrograph of muscle layers taken through *A* in *1* to demonstrate collection of India ink particles.

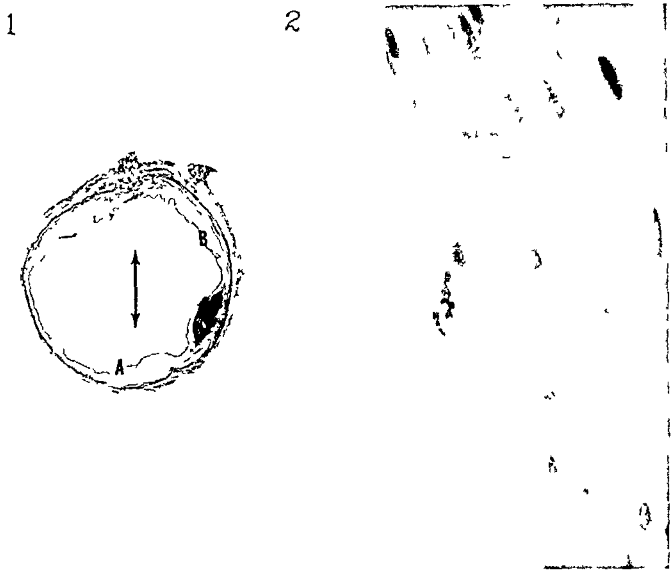

Fig 6 *1*, Coronal section of bladder illustrating injection site of India ink suspension 1 cm to left of midline (arrows) Suspension has dispersed to *A* and *B* within lymphatics of muscle layers *2*, Photomicrograph of muscle layers taken through *A* in *1* demonstrating collection of particle filled cells

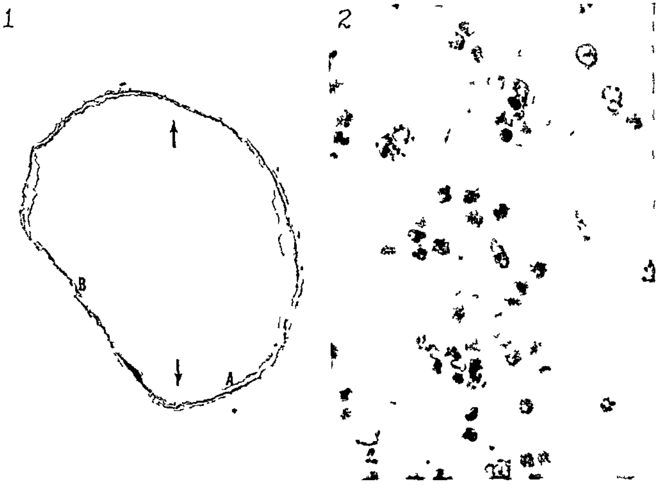

Fig 7 Coronal section of bladder illustrating injection site of India ink suspension 1 5 cm to right of midline (arrows) Radial dissemination has occurred to points *A* and *B* *2*, Photomicrograph of adventitial layer taken through *A* in *1* to illustrate many discreet particle filled macrophages

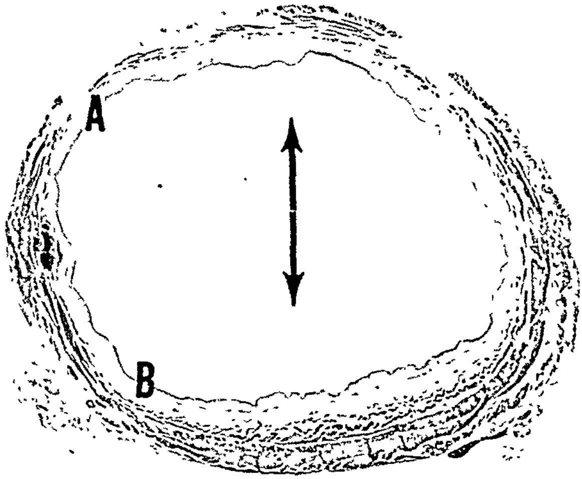

Fig. 8. Coronal section of bladder demonstrating India ink injection site in right lateral wall. Arrows indicate midline. Particles of suspension have disseminated anteriorly to *A* and posteriorly to *B*.

Right upper quadrant: The suspension had been injected at a point 1.5 cm. from the posterior midline. Radial dissemination involved 25 per cent of the total bladder circumference. Particles crossed the midline posteriorly. These findings are demonstrated in figure 7. No nodes were involved.

Lateral Bladder Walls

Right lateral wall: The suspension had been injected in the right lateral wall at a point midway between the bladder neck and the dome. Radial spread occurred in either direction to involve approximately 35 per cent of the total bladder circumference (fig. 8). No particles crossed the midline. The right common iliac node was grossly involved with particles.

Left lateral wall: Findings were similar to those observed in the right lateral wall. The left common iliac node was grossly involved with India ink particles.

DISCUSSION

India ink injected into the bladder of the dog is not cancer growing in a human bladder. It would be scientifically injudicious to infer too great clinical significance from the results illustrated by this experiment. Some clinical observations of other investigators referred to previously concerning the spread of bladder cancer have been substantiated by this work. In some instances these observations have been extended. Powell has demonstrated the simple anatomy of the lymphatics in the postmortem bladder. The experimental data now presented report for the first time the functional mode of spread of a large molecule colloidal suspension injected into the bladder submucosa of the living subject.

Dissemination of large colloidal particles from site of submucosal injection occurred by means of the macrophages within the lymphatic channels. In nine of the ten dogs studied, such macrophages could be visualized throughout the submucosa, muscle and adventitial layers in the area immediately deep to the site of injection. *Microscopic examination of the total circumference of all the* specimens failed to demonstrate colloidal particles within the mucosa, and only minimal radial invasion of the submucosa. In each instance, the most distant spread took place within the lymphatics of the muscle planes and to a lesser extent in the adventitial layer. Primarily, the India ink particles disseminated within the lymphatics through the submucosal and muscular layers to the adventitia, and secondarily in a radial manner within the muscle. Powell illustrated such an anatomical arrangement in human bladders. He described a staircase type of lymphatic drainage beginning in the submucosa in small collectors which progressed through the muscle layers in larger vessels to the adventitia, where they joined larger collectors.

In the present experiment suspension particles travelled in either direction, irrespective of the site of the original injection. In all sections studied, the dissemination involved approximately 25 to 50 *per cent of the total bladder circumference*. This spread was not necessarily unilateral, but instead crossed the midline either anteriorly or posteriorly except when the site of injection was on the lateral wall of the bladder. This physiological observation is not entirely consistent with the anatomical observations of Powell and also Arguello Cervantes.[5] They observed relatively little lymphatic anastomosis across the anterior midline in the human bladder, but a profuse one across the posterior midline.

This experiment demonstrated that lymph node involvement occurred in six of ten dogs studied. In five of these dogs, the drainage was ipsilateral, in one, contralateral. The contralateral involvement was observed in the dog whose bladder had been injected in the midline anteriorly. Marshall, in his study of 104 cases of vesical neoplasm treated by radical cystectomy, reported that in all instances in which the carcinoma was well away from the midline, that when nodes *were involved* with metastases, they *were ipsilateral*. Lesions near the midline seemed capable of metastasizing to both sides. This author has not distinguished between anterior and posterior lesions in reference to this problem. The experimental evidence now reported is strongly in favor of a contralateral lymphatic spread anteriorly and posteriorly within the bladder. Contralateral lymph node involvement was not observed. This fact confirms Marshall's clinical impression concerning ipsilateral lymphatic spread of these tumors. Vesical neoplasms do not spread within the bladder by way of the lymphatics only, nor do they metastasize extravesically by that route to the exclusion of other methods of diffusion, such as vascular or local contiguous invasion. In the live experimental animal there appears to be considerable contralateral lymphatic spread within the bladder which should be considered as a potential mode of invasion to contralateral lymph nodes.

It is significant to note that in only one of four dogs whose bladders were injected on the posterior surface, were the colloidal ink particles taken up by the pelvic nodes. Both lateral, and three of the four anterior bladder areas, drained particles to the nodes. This feature is in agreement with the clinical impression of Jewett that channels from the posterior vesical surface are longer, and therefore the nodes which drain such areas are involved more slowly than from corresponding lesions on the anterior surface. In each of the instances mentioned, in which nodes were not involved, India ink particles had disseminated into the bladder muscle and adventitial layers.

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As a result of these observations it would appear that it is highly possible and even probable that a superficial bladder cancer, i.e., one that has not even invaded the muscle, will spread beyond the bladder. The size (area) of the lesion invading mucosa is apparently not of as great significance as the degree of submucosal involvement. This fact is based on the observation that there is little, if any, phagocytic and no lymphatic spread within the mucosa itself. In view of these experimental data, perhaps there should be a re-evaluation of the clinical impression that all bladder cancers not invading the muscle layers, are potentially curable.

Six of the ten submucosal injections produced involvement of regional nodes. If the analogy is comparable, then simple cystectomy or segmental resection for noninvasive vesical cancer that does not include lymphadenectomy, would fail to eradicate the disease in a large percentage of cases. In point of fact, at least 15 to 26 per cent of patients with noninvasive bladder cancer are not cured by any procedure now practiced. Taussig[9] and Meigs[10-13] observed in large series of patients with *early* carcinoma of the cervix that at time of operation, lymph nodes were grossly or microscopically involved with tumor cells in 17 to 25 per cent of cases. Consequently, these investigators have recommended radical lymph node dissection in combination with either radiation therapy or radical hysterectomy in such cases.

Four out of ten dogs in the present experiment had no nodal involvement. In addition, the spread of ink particles involved 25 to 50 per cent of the total bladder circumference in the sections studied. On the basis of these findings, it would appear that if segmental resection was elected as the therapeutic procedure, then such a resection should be a radical operation involving excision of at least one-half of the bladder in addition to the previously recommended lymphadenectomy.

SUMMARY

When a colloidal suspension of India ink particles was injected into the submucosa of the bladder of the dog, the particles disseminated by way of macro-

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phages within the lymphatic system Particles of solution were not observed within the mucosa Dissemination occurred locally within submucosa, muscle and adventitia Radial diffusion was most distant in the muscle layers Particles invaded the muscle layer for equal distances in either direction to involve 25 to 50 per cent of the total bladder circumference and crossed the midline anteriorly or posteriorly except when the site of injection was on the lateral wall of the bladder Lymph nodes were involved in six of ten dogs studied In five of these dogs, drainage was ipsilateral, in one, contralateral In only one of the four dogs, whose bladders were injected on the posterior surface, was the India ink taken up by the nodes Three of the four anterior areas, and both lateral areas, drained particles to regional lymph nodes

In view of these experimental data, perhaps there should be a re evaluation of the clinical impression that all bladder cancers involving the mucosa, submucosa and superficial muscle layers, are potentially curable by surgery confined only to the bladder Six of the ten submucosal injections produced involvement of regional nodes If the analogy is comparable, then any surgical procedure that fails to include lymphadenectomy would fail to eradicate the disease in a large percentage of these cases

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CONSIDERATION OF SOME BIOPHYSICAL FACTORS IN DISTENTION OF THIN-WALLED HOLLOW VISCERA

JOHN D. LAWSON, CAPT. (MC, USA) AND WILLIAM B. TOMLINSON, CAPT. (MC, USAF)

From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania, Philadelphia, Pa.

In 1903, Kelling inflated rubber balloons and noted that the pressure rose early during distention. Following this initial rise in pressure the pressure gradually decreased during distention until just before rupture of the balloon, at which time the pressure dropped precipitously.

In 1909, Osborne made similar observations on balloons and on extirpated canine bladders.

Recently we have demonstrated similar pressure-volume curves in dogs and man during acute urinary retention.

There have been several notable attempts to explain the paradoxical pressure-distention curves obtained on distention of thin-walled, elastic, hollow spheres. In 1910 Frank proposed the following formula for pressures developed during distention of hollow, thin-walled, elastic spheres, which followed Hooke's Law perfectly: $P = 4Ed_0\, r_0 \left(\frac{r - r_0}{r^3} \right)$

Where P = pressure, E = Young's Modulus, d_0 = wall thickness before stretching occurs, r = radius, r_0 = radius at which stretching begins to occur.

Brody and Quigley (2) by similar reasoning arrived at the following formula: $P = 4Ed_0 \cdot \frac{r - r_0}{r^2}$.

These equations were derived in the following manner: from the definition of Young's Modulus of Elasticity E, the tension T, per unit of cross sectional length of an elastic strip which has thickness d, and has been stretched to length l, from the resting length l_0 will be: $T = Ed\ (l - l_0)/l_0$

When this formula is applied to a lune cut from a thin-walled hollow elastic sphere the equation becomes:

$$T = E\ (\text{man})\ d\ (r - r_0)/r_0$$

This manifest modulus of elasticity is necessary because the lune is stretched equally in all directions along the spherical surface—not unidirectionally. Frank, Brody and Quigley all agree that E (man) $\approx 2E$. Therefore the final formula representing the elastic characteristics of such a lune during distention becomes:

$$T = 2Ed\ (r - r_0)/r_0$$

Substitution of the above formula in the formula for pressures developed within a hollow sphere $P = 2T/r$ (cf. Winton and Bayliss, p. 305) (12) yields: $P = \frac{4Ed}{r_0} \cdot \frac{r - r_0}{r}$

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Frank notes that wall thickness is inversely proportional to the square of the radius and therefore assumes $d = (r_0^2/r^2)d_0$ At this point there is disagreement for while Brody and Quigley agree that true wall thickness varies in the inverse quadratic manner described by Frank, they note that the actual number of elastic fibrils per unit length is inversely proportional to the *first* power of the radius Therefore they believe that the effective value d is actually equal to $(r_0/r)d_0$

In the two mathematical developments shown above it will be seen that as a perfectly elastic thin-walled hollow sphere distents, the peak of pressure occurs at $r = 3/2r_0$ (Frank) or $r = 2r_0$ (Brody and Quigley) Thereafter in both cases, the pressure approaches zero asymptotically as the sphere distends

We have shown that during acute urinary retention the urinary bladder follows curves similar to those developed mathematically by Frank, Brody and Quigley It appears therefore that the descending portion of the pressure distention curve observed in the urinary bladder is not entirely due to fatigue or relaxation, but most likely to the physical stretch characteristics of the bladder

There are other factors which obviously affect the immediate distention characteristics of thin-walled, hollow, spheroid viscera For instance, while recording a cystometrogram, distention sets up reflexes which cause irregular bladder contractions These contractions do not in themselves alter the *overall* curve characteristics obtained This is obvious when one compares the curves obtained during in vivo experiments with those obtained during Osborne's experiments on extirpated bladders

If a thin-walled, hollow sphere of perfect elasticity is distended, the rate of distention should have no effect on the curves produced The pressure distention curves of the urinary bladder, however, vary greatly in shape as a result of varying the rate of distention and indeed even as a result of changes in the constancy of the rate of distention This fact becomes clinically significant when one realizes that the rate and constancy of filling of the urinary bladder are the prime determining factors with regard to whether or not extravasation of the distending fluid into the peritoneal cavity will occur Hence, as urinary bladder pressure increases during acute urinary retention, the kidneys become oliguric—a factor which reduces the height to which bladder pressures rise and thereby prevents the extravasation of urine into the peritoneal cavity

In dealing with biologic structures one must constantly consider the changes in the stretch characteristics of these structures when they are involved in some pathologic process For example, urinary bladders which have been greatly distended frequently become fibrotic, and subsequent to this fibrosis the stretch characteristics of the bladders involved are greatly altered Indeed, in some cases of bladder fibrosis, there is no evidence of peak pressure followed by a descending pressure as distention proceeds, but rather, the pressure increases irregularly until the final rupture of the bladder occurs at unusually high pressure (roughly twice the pressure observed during retention in normal bladders)

During the distention of thin-walled, hollow viscera one occasionally notes that all parts of the viscus do not distend equally For example, Giunturco demonstrated that "receptive relaxation" of the cat's stomach is due principally to the distention of the fundus. We have observed that as dogs' urinary bladders are distended, the domes of the bladders seem to contribute most to the distensibility; for if one examines a bladder which has been greatly distended, there are more submucosal thromboses and hemorrhages in the dome.

An observation which may be of some significance is the similarity of the pressure-distention curves of balloons or urinary bladders to the curve which represents Starling's Law of the Heart. It may well be that the failing heart has altered stretch characteristics which in themselves may be important contributing factors to the maintenance of cardiac failure. The fact that digitalis decreases the diastolic size of the failing heart may well indicate that there is a change in cardiac stretch characteristics with shortening of the cardiac fibers and a subsequent more forceful cardiac contraction with more efficient oxygen utilization per unit of cardiac work.

Cournand et al. note that the pressure in the left auricle is greater than that in the right auricle in patients with interauricular septal defects. Altschule notes that this pressure differential probably accounts for the flow from the left to the right auricle in such cases: Little et al. attempted to determine the cause of this pressure difference and made observations on the volume-elastic characteristics of the right and left atria. They concluded that this pressure differential between the left and right auricles could be explained on a mechanical basis since the stretch characteristics of the two auricles vary considerably. At identical volumes the left auricle had a higher pressure than the right auricle.

Finally, Courvoisier's law of the gallbladder may be explained on a primarily physical basis if one notes the primary differences in obstruction occurring from stones versus that occurring from carcinoma. In the case of stones the obstruction is intermittent and for relatively short intervals the pressure may become quite high. Hence we may have the counterpart of the repeatedly distended urinary bladders which subsequently become fibrotic and whose volume when fibrosed is small. In the case of carcinoma the obstruction is relatively constant in development until obstruction becomes complete, allowing more time for gallbladder distention. In this case the gallbladder cannot fibrose at a small volume as might occur if the obstruction were temporarily relieved as it is in the case of obstruction due to stone. The very large gallbladders seen occasionally in carcinoma of the head of the pancreas may be on the descending portion of the pressure-distention curve and so continue to dilate although less and less pressure is necessary to cause further dilatation.

Of course gallbladder infection secondary to stones should be borne in mind, but it is unlikely that one could explain all cases of small thick-walled gallbladders seen in cases of stone obstruction on the basis of infection. Mechanical factors such as the mode of obstruction and the stretch characteristics of the gallbladder should be considered in any given case.

SUMMARY

Pertinent mathematical concepts which have been developed, for thin-walled, hollow elastic spheres have been reviewed.

Rapidity of distention of hollow viscera is an important determining factor in the type of pressure-volume curve obtained in bio-physical work.

The constancy of the rate of distention is an important determining factor during the distention of a biologic structure.

The stretch characteristics of biological structures such as the heart, urinary bladder, stomach, and gallbladder are of clinical significance in various disease states.

Since one can determine the modulus of elasticity for a substance composing a balloon by analyzing the pressure distention curve produced during distention, it would seem to follow that an effective modulus of elasticity could be found for biological structures by analyzing their pressure distention curves. In actual practice, however, such variables as constancy of distention, rapidity of distention and the portion of the viscus contributing most to the distensibility makes the interpretation of such curves difficult if not impossible. Likewise, if the characteristics of such structures are determined under one set of conditions and assumed to be constant characteristics, many false concepts may be entertained as to the physical characteristics obtaining in various physiologic states.

Finally, it is our opinion that not enough emphasis has been placed on the purely mechanical characteristics of various hollow viscera, particularly with regard to the unique characteristics which are displayed by some of these important structures.

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A SIMPLE METHOD FOR REDUCTION OF PARAPHIMOSIS

CAREY N. BARRY

From the Department of Surgery, Division of Urology, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.

It is the purpose of this paper to introduce a simple atraumatic method for the reduction of paraphimosis. It has been found to be the most efficacious method in children especially because of its simplicity and reduction in manipulation. A review of the literature offers the methods of 1) gradually increasing manual pressure and reduction with or without additive use of ice packs and 2) when pressure fails "dorsal slit."

Our method employs the old and oft used technique of reduction of edema by Southey tube drainage. If ice packs and/or manual pressure fail, several hypodermic needles (3 are usually sufficient), No. 20 gauge, are introduced directly into the edematous ring after employment of local antiseptics. No local anesthetic has been found to be necessary. The edema fluid, under considerable tension, will drip from the needle ends which if properly directed need no support. After a few moments a marked reduction is noted in the edema and upon withdrawal of of the needles the prepuce may be easily brought over the glans. Penicillin, 400,000 units, and streptomycin, 1 gm., are then administered.

The patient is then returned for an interval circumcision without having been subjected to previous incision and suturing.

The author has used this method on two occasions. By personal communication, Dr. Bithel Wall of the Department of Urology, Medical College of Georgia, informs me of two successful cases in his hands, both of which had resisted all other methods and attempts at reduction (except dorsal slit).

Richards Professional Bldg., Fort Myers, Fla.

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BALANITIS XEROTICA OBLITERANS: A CASE REPORT

H. K. TURLEY AND JOHN L. SHAW

Stuhner, in 1928, used this term to describe a chronic, progressive, atrophic, sclerosing process of the glans penis and prepuce which frequently eventuated in urethral stenosis.

Freeman and Layman, in a study of 18 cases, found that the disease can occur at any age and does not necessarily follow operative procedures as previously believed. By 1944, Frishwasser and Finkle reported a total of 24 cases and added one of their own. In 1947, Farrington and Garvey reported two additional cases. It is believed that this condition is certainly not so rare as previous reports in the medical literature would indicate.

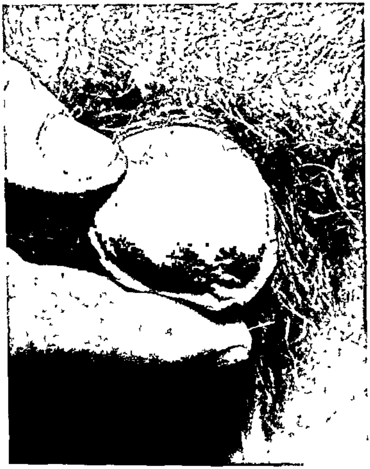

FIG. 1

In review of various case reports these lesions are usually asymptomatic, however, there may be a bewildering variation of symptoms in which the most prominent are: obstruction, pruritis, pain, and purulent discharge. The usual gross description is as follows: waxy white, macular, sharply marginated, slightly infiltrated, non-ulcerative lesion extending into the urethra for about 4 mm. (fig. 1).

Balanitis xerotica obliterans is a dermato-urological problem. Its importance lies in its recognition and differentiation from more serious conditions and maintenance of the urethral opening. Freeman and Layman believe that it is synonymous with kraurosis penis. It should be distinguished from erythroplasia of

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Queyrat and leukoplakia which are hypertrophic processes. It can be easily confused with lichen sclerosis et atrophicus, lichen planus and carcinoma. The usual treatment is mild emollients, urethral dilation when needed and surgical resection if necessary for diagnostic purposes.

Reporting a case on a 44 year old white man who had noticed an infiltrative, ivory-white growth in the urethral meatus for the past 4 months. This lesion had been asymptomatic with the exception of a gradual closing of the urethral meatus. A wedge of tissue was removed from the ventrum of the urethral meatus for histological study and to mitigate the stenosis which had progressively obliterated the orifice. Urethral dilatations were done for a one month postoperative period. This patient has now been followed for approximately 6 months. There is no evidence of recurrence and the urethral meatus has remained adequate.

SUMMARY

A brief summary of previous case reports and descriptions of balanitis xerotica obliterans is given.

An additional case report is presented.

We wish to thank Dr. Fox Miller, dermatologist, for his collaboration in the diagnosis and treatment of this patient, also Dr. Merlin L. Trumbull and Dr. W. T. Snoddy, pathologists of the Baptist Memorial Hospital, Memphis, Tenn. for establishing the histological diagnosis. Dr. Zola K. Cooper, Department of Pathology, Washington University School of Medicine, St. Louis, Mo. was kind enough to confirm the diagnosis from the histological sections.

899 Madison Ave., Memphis 3, Tenn.

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ANOMALIES AND COMPLICATIONS OF THE UROGENITAL TRACT ASSOCIATED WITH CONGENITAL IMPERFORATE ANUS

HARRY M SPENCE

From the Urological Departments of the Dallas Medical and Surgical Clinic, Children's Medical Center, and Parkland Hospital, Dallas, Texas

Of the 44 cases of congenital imperforate anus seen at Texas Children's Hospital and Parkland Hospital since 1946, fifteen or approximately one third have exhibited some major urological disorder This complicating urological component of any given case of imperforate anus may arise in one of three ways: 1) by coincidence, with no direct relationship other than the tendency of congenital anomalies to be multiple, 2) from faulty embryological development of the primitive hindgut with persistence of a cloaca or the formation of a recto-urethral fistula, and 3) through operative accident in the surgical correction of the original condition

TABLE I

Etiology	
Coincidental	3
Faulty embryology	10
Operative injury	2
Type	
Recto urethral fistula	5
Rectovesical fistula	2
Persistent cloaca	5

The incidence of these mechanisms and the aberrant communications found in my series are shown in table 1 In addition urinary infection and ureteral obstruction caused by massive fecal impaction from a poorly functioning reconstructed anal outlet, may further complicate the problem (fig 1) Certainly all who deal with cases of imperforate anus must be constantly on the alert for the occurrence of urological complications

EMBRYOLOGY

The normal embryogenesis of these parts is shown in figure 2 The downward growth of the urorectal septum divides the primitive cloaca into the bladder and urogenital sinus ventrally and the rectum dorsally At about the time this partition is completed, the cloacal membrane ruptures to provide separate outlets for the urogenital tract anteriorly and the rectum posteriorly Failure of the latter orifice to develop results in the condition designated by the clinical term "imperforate anus" The rectal pouch may terminate blindly at either a low or a comparatively high level The possible varieties of fistulous communication with the urogenital tract are a rectovesical fistula, a recto urethral fistula, or a persistent cloaca (fig 3)

Read at annual meeting, American Urological Association, St Louis, Mo May 13, 1953

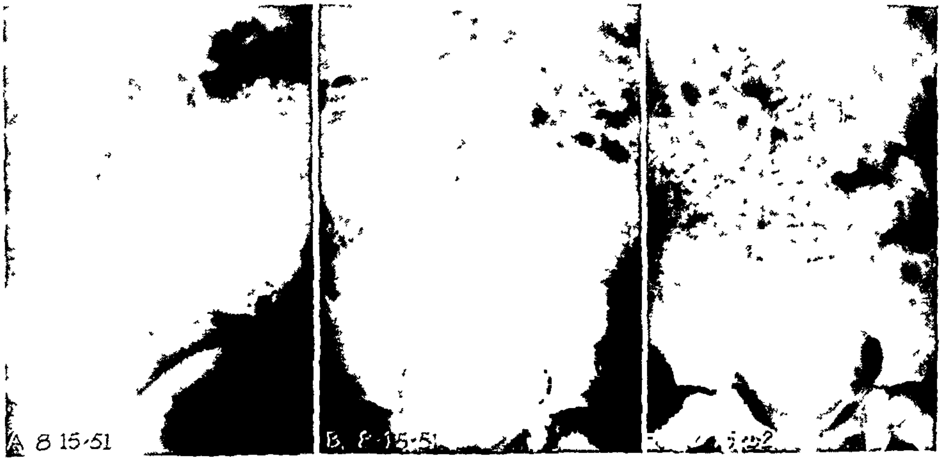

FIG 1 A and B, excretory urograms showing fecal mass causing bilateral ureteral obstruction in a child with a poorly reconstructed anus C, improvement in urograms after adequate bowel outlet established by "pull-through" technique.

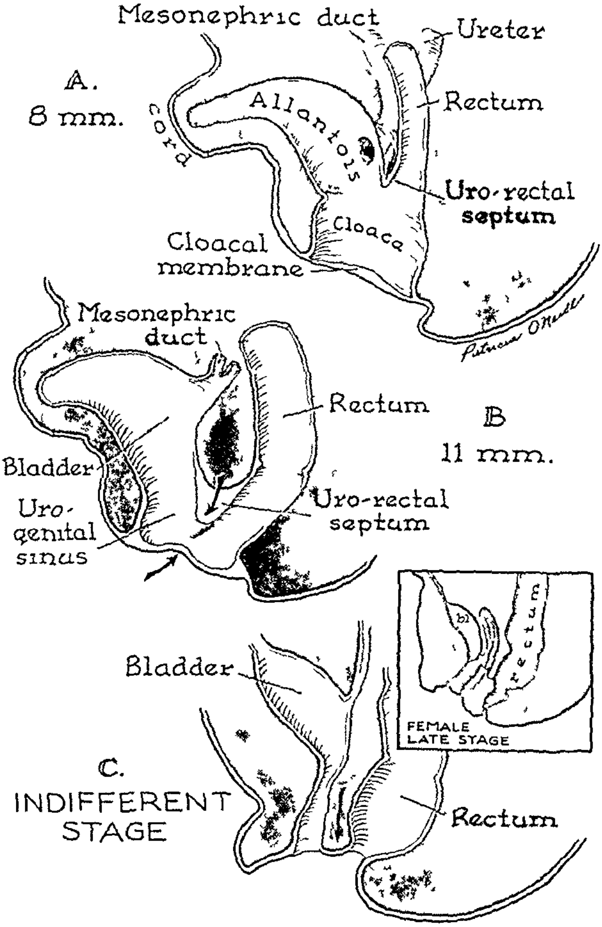

FIG 2. Normal embryological development

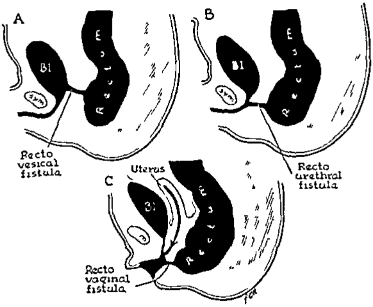

Fig 3 Types of fistula found

CLINICAL PICTURE AS IT CONCERNS THE UROLOGIST

Excluding for the moment the cases in which the urological abnormality is merely co incidental, the clinical findings will depend upon the age at which the patient with imperforate anus is first seen, and the surgical procedure to which he may already have been subjected The passage of urine per rectum or of gas and/or feces per urethram consititutes prima facie evidence of abnormal communication between the genito-urinary and intestinal tracts In the newborn, meconium may exude from the external urinary meatus, but its absence does not exclude the possibility of a fistula being present Not infrequently the fistulous communication is first discovered by the surgeon when a gush of urine is encountered while he is freeing up the gut either from below or above

If no such urological component is apparent at birth or evident at operation performed during the neonatal period, and if a satisfactory bowel outlet is present, several weeks, months, or even years may elapse before these cases come to the attention of the urologist Signs and symptoms of chronic or recurrent urinary tract infection, often with an obstructive element, may bring the patient in at this stage, and it is here that co incidental urinary tract anomalies should be suspected In several of our cases, advanced renal damage had occurred before it was realized that the cause of the child's ill health lay in the urinary tract Likewise an overlooked recto urethral fistula of either congenital or acquired type, may become apparent only after a considerable period of time when feces appear in the urine or vice versa True cloacal defects are readily recognizable at the initial examination

TREATMENT

Until recently, the preferred method of correction of the imperforate anus itself has been by the perineal route whenever possible In some instances, simple incision of the imperforate anal membrane has sufficed, but in most cases a more extensive perineoplasty has been required to bring the blind ending rectal pouch down to the perineum to establish normal anorectal relations In case this was found to be impossible of accomplishment from below a sigmoid colostomy was

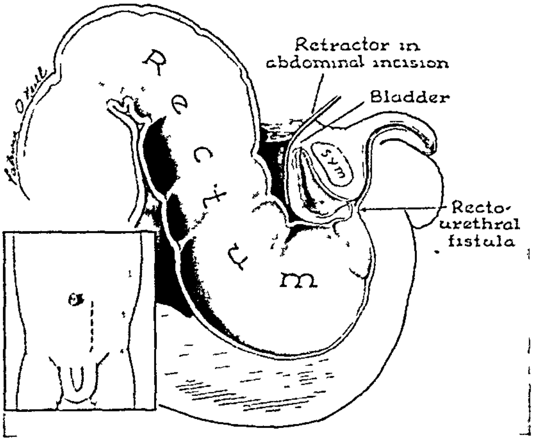

FIG. 4. "Pull-through" operation (after Norris) Abdomen opened; rectum found terminating in urethra.

done and the proctoplasty deferred until the age of two or three years. The ease with which a urethral injury might take place or a fistula be overlooked by the perineal approach in the newborn is readily apparent. The difficulty one might experience in excising and closing such an opening is also obvious.

In 1949 Norris proposed a one-stage combined abdomino-perineal "pull-through" type of operation, as illustrated in figures 4, 5 and 6. Through the opened abdomen the bowel is dissected from the pelvic floor downward until the blind rectal end is isolated. A clamp is then inserted through a short perineal incision in the estimated center of the sphincteric area, and the rectum drawn out through this and sutured to the skin of the perineum. In my opinion the "pull-through" operation is particularly adapted to the early correction of preexisting recto-urethral fistula (fig. 3, *B*). Likewise, the hazard of producing such a fistula accidentally is less than in the conventional perineal procedure.

When these distressing cases come to the attention of the urologist compara-

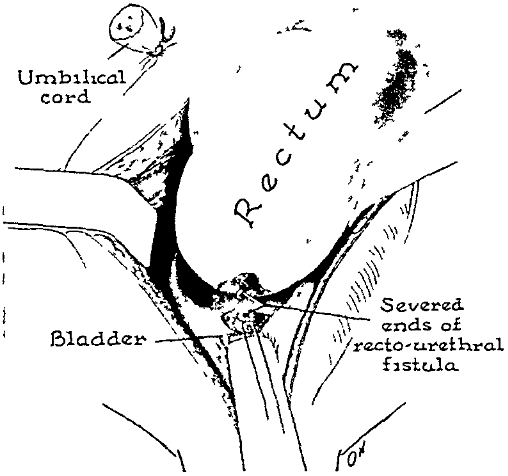

FIG. 5. Second step of operation. Fistula severed and urethral opening closed

tively late in their course, often after one or more operations have already been performed, they represent most difficult problems. At this point each case must be individualized, and no hard and fast rules of management can be laid down. In general terms, carefully planned stage procedures should be carried out, directed at preservation of renal function by relief of obstruction, complete separation of the urinary and bowel channels, the establishment of bladder and rectal continence, and correction of external genital deformities. The aims of the operation are listed in their approximate order of importance.

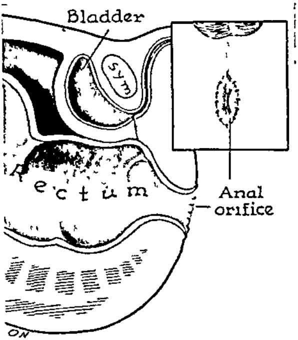

FIG. 6. Third step in which bowel (after emptying) is pulled through perineal incision.

Before embarking on any operative attack, one is well advised to make as accurate a diagnosis as possible of the exact conditions present. This is best achieved by an unhurried local examination under anesthesia, combined with cysto-urethroscopy, endoscopy of the bowel, urography, and roentgenographic bowel studies.

SURVEY OF A PERSONAL SERIES OF 15 CASES

In my series of 15 cases, the relationship of the urological abnormality to the imperforate anus was regarded as co-incidental in three patients, all males, and consisted of a bladder neck obstruction with bilateral hydronephrosis in two and of a massive unilateral hydronephro-ureter in the third. In an additional five cases the presence of only one kidney could be demonstrated and a diagnosis of unilateral renal agenesis seemed warranted.

In the remaining 12 cases some type of abnormal communication between the rectum and lower urogenital tract was present. In five males this opening took the form of a recto-urethral fistula. Of these, three obviously were due to faulty embryological development, while in two the fistula probably resulted from surgical trauma at the time of the anoplasty. Lastly, 7 cases were encountered in which some variation of a persistent cloaca was found. Four of these were females in whom, in addition to a rectovaginal fistula, the urethra and vaginal outlet were malformed, so that urine and feces were admixed in a common pouch before being expelled through a single opening. Three males were considered to have had a persistent cloaca. The rectal pouch ended in the bladder in two of these, and in the third discharged through a midscrotal hypospadiac opening.

CASE REPORTS

An example of a coincidental condition follows.

Case 1. J. B. C., Texas Children's Hospital No. 150. An attempt to enter the bowel from below on the first day of life was unsuccessful in this male infant, so a double-barrel colostomy was done, which worked satisfactorily. During the following months the child did poorly and had numerous febrile attacks during one of which pus was found in the urine. At seven months of age, a complete urological study was carried out revealing a normal right kidney and a marked left hydronephrosis and hydro-ureter, apparently due to a constriction at the left ureterovesical junction (fig. 7, *A*). A nephro-ureterectomy (fig. 7, *B* and *C*) restored the child to health. Subsequently a successful anal reconstruction was done.

The next two case reports illustrate the management of urethrorectal fistulas following operative injury at the time of the original anoplasty.

Case 2. D. A., Texas Children's Hospital No. WW-835. A 6 months old boy had passed a mixture of urine and feces intermittently from both the anus and urethra following perineal anoplasty. Complete urological study revealed a urethro-rectal fistula (fig. 8). He was cured by the conventional Young-Stone-Whitehead procedure (such as is employed for repair of recto-urethral fistula after perineal prostatectomy) whereby a sleeve of rectum was brought out through the perineum so that the original defect in the bowel wall came to lie outside the skin margin.

Case 3. M. D. F., Texas Children's Hospital No. 7255. The findings in this 5 year old boy are shown in figures 9 and 10. Apparently the urethra had been

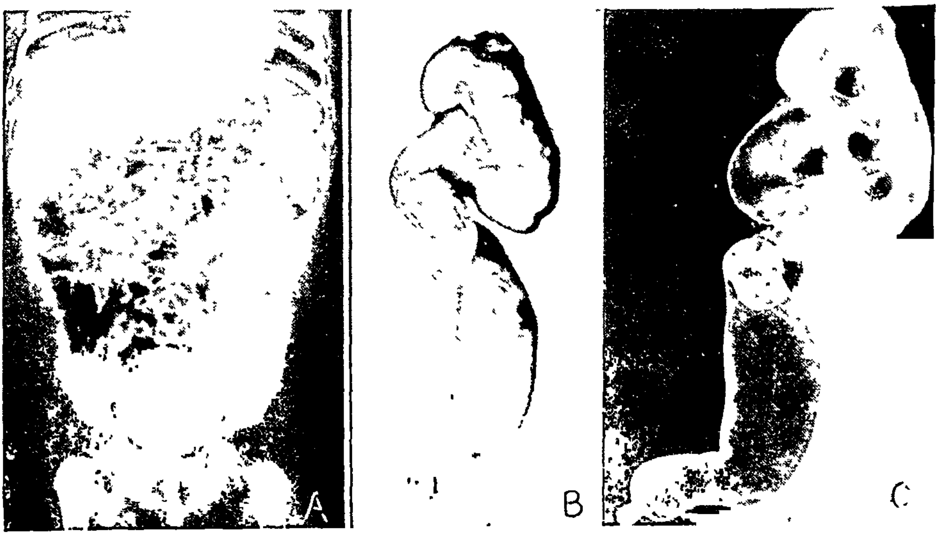

FIG. 7. Case 1. *A*, preoperative pyelo-ureterogram. *B* and *C*, surgical specimen

completely transected when he was operated upon 6 hours after birth. All urine passed through a non-sphincteric anus. Complete perineal dissection permitted anastomosis of the two ends of the urethra over a splinting catheter with successful restoration of its continuity and surprisingly good urinary continence. An incidental finding was a congenital solitary kidney.

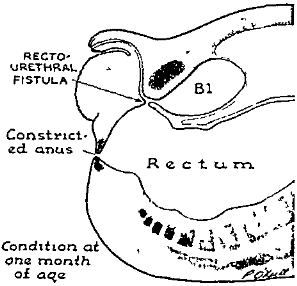

FIG. 8. Case 2. Recto-urethral fistula resulting from injury at time of anoplasty. Successfully repaired by Young-Stone-Whitehead procedure.

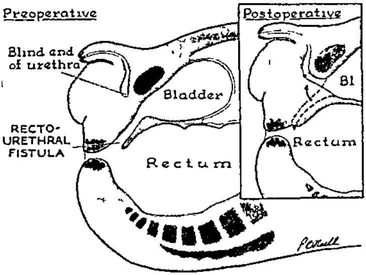

FIG. 9. Diagram of findings in case 3 where urethra had been completely cut across at initial operation

The following three case reports are representative of anomalies due to faulty embryological development. Case 4 is that of a rectovesical fistula, while cases 5 and 6 illustrate persistence of the cloaca in a female and male respectively.

Case 4. D. H., Parkland Hospital No. 84508. A loop colostomy had been done a few hours after birth on this male infant. At the end of 48 hours no urine had been voided so the infant was catheterized and meconium but no urine was obtained. An opaque cystogram showed reflux up the distal segment of the colostomy loop which was confirmed by injecting indigo carmine through the catheter, noting its appearance at the colostomy opening. Blood urea was 122 mg. per cent. The child died 5 days after birth and on postmortem right kidney and ureter were found to be absent. The left kidney was represented by an enlarged hydronephrotic

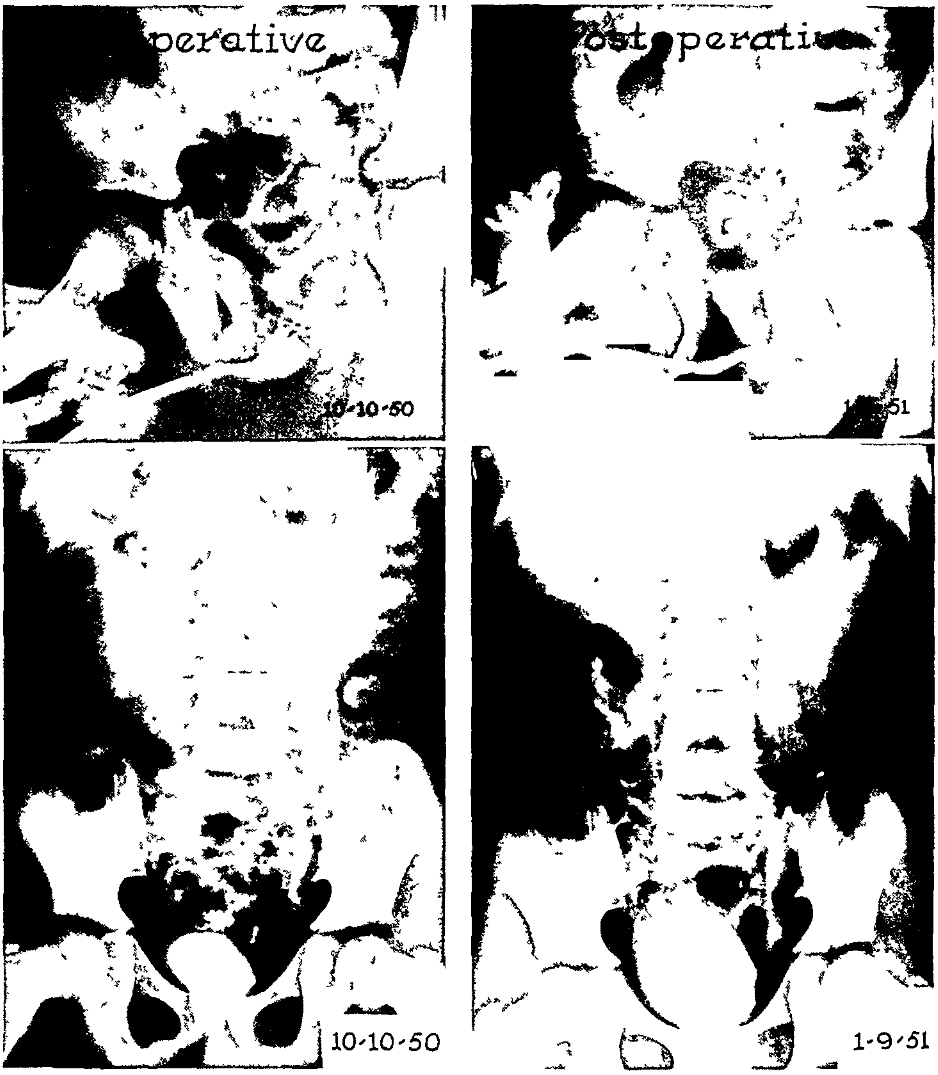

Fig 10 Case 3 Preoperative (upper left), blind ending of urethra in bulb shown on urethrogram Note reflux of dye into pelvic veins Lower left, solitary kidney, small low-lying bladder Postoperative (upper right), urethral continuity established Lower right, larger, more normal-appearing bladder

sac with a dilated and tortuous ureter The distal end of the colon opened into the base of the bladder, forming a rectovesical fistula. (fig. 11).

Case 5. K. B., Texas Children's Hospital No. XX-557. A 2½ year old girl dribbled urine and feces continuously through a common perineal orifice There was marked excoriation about the genitalia. After several unsuccessful attempts by other methods, this case was solved by doing a Norris "pull-through" type operation which completely diverted the fecal stream and permitted reconstruction of the urethra from the anterior vaginal wall. (fig. 12).

Case 6. C. H , Parkland Hospital No. 81452. A 41 year old man had never sought medical attention prior to his admission for right abdominal pain He had been born with an imperforate anus, and throughout his entire life had passed all

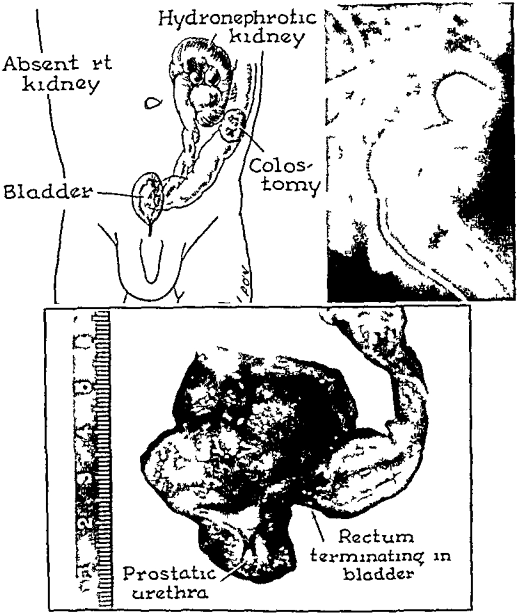

FIG 11 Case 4 (Left) findings at autopsy (Right), on making a cystogram the radiopaque dye flows into distal segment of bowel (Below), photograph of autopsy specimen

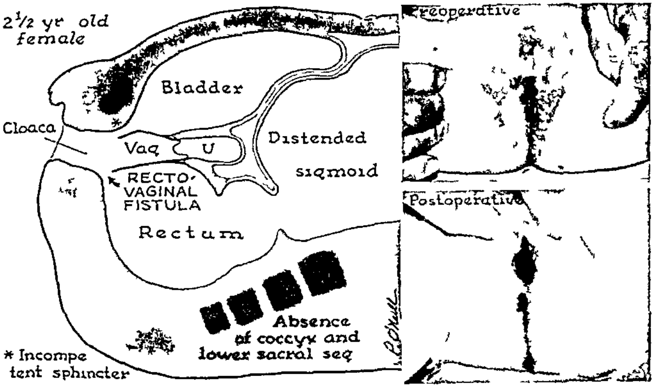

FIG 12 Case 5 (Left), schema before definitive anoplasty (Right), appearance of genitalia before and after cloaca was abolished

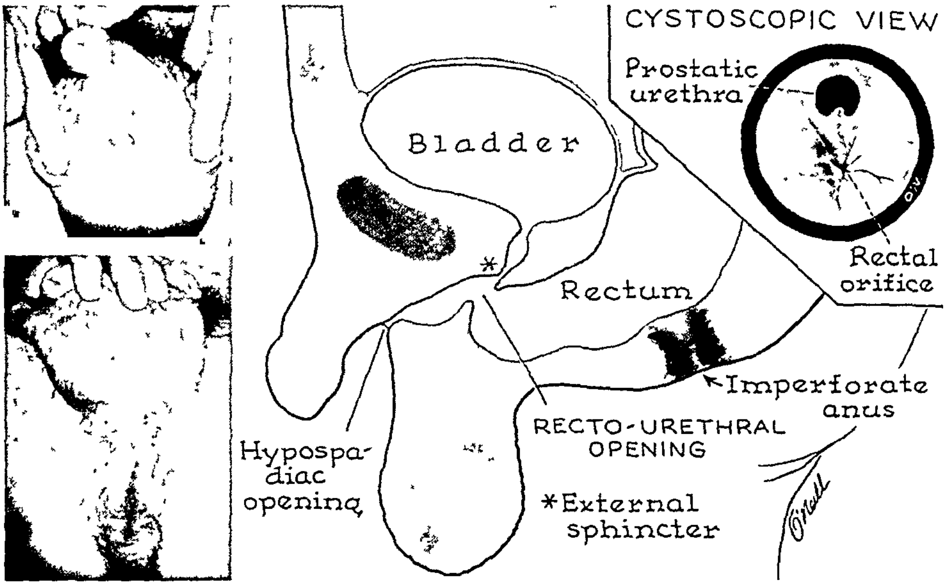

FIG. 13. Case 6. At left (above) penoscrotal hypospadias through which all excreta passed. (Below), imperforate anus. Diagram shows abnormal communication.

excreta through the hypospadiac opening shown in figure 13. He was continent of both urine and feces. The remarkably normal appearance of the upper urinary tract is shown in figure 14, *A*. The urethrogram (fig. 14, *B*) demonstrates the separate openings of the prostatic urethra and the bowel into the bulbous urethra. No operation was recommended in this case as I doubted my ability to improve the satisfactory functional result he had enjoyed for 41 years.

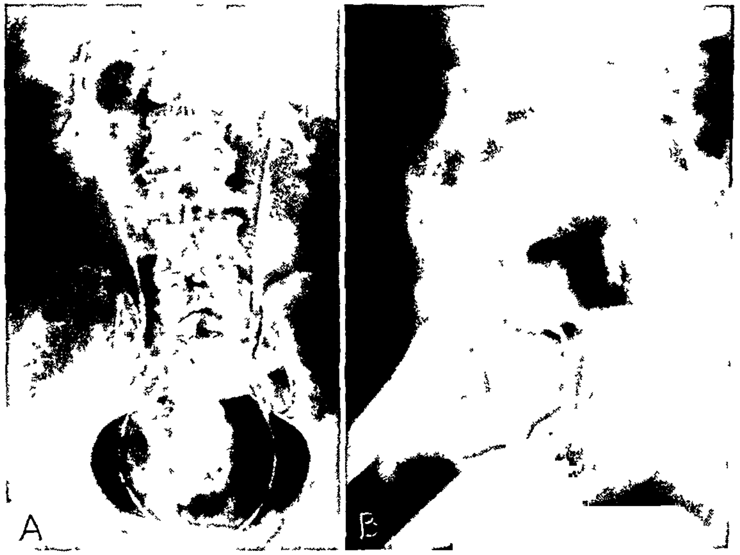

FIG. 14. Case 6. *A*, normal retrograde pyelogram. *B*, urethrogram through hypospadiac meatus showing prostatic urethra and rectal aperture.

SUMMARY

Typical ureterovesical and vesical neck obstruction may occur by chance as a concurrent congenital defect not directly related to the bowel atresia Failure of the infant to do as well as might be expected after successful relief of the intestinal tract obstruction should call for prompt urological study, especially if pyuria is present Treatment here consists of correction of the primary urological disorder by the usual standard technique

The characteristic genito urinary anomaly associated with imperforate anus consists of some form of abnormal communication between the lower intestine and the genito urinary passages, and is caused by failure of the urorectal septum completely to partition the two channels The possibility that the communication may have resulted from accidental opening of the urethra or bladder at the time of anoplasty must be borne in mind Depending on the location of the fistulous communication, and on the sex of the individual, the patient may exhibit 1) a rectovesical fistula, 2) a recto urethral fistula, or 3) some variety of persistent cloaca The first two types occur predominantly in males, the last is more common in females

The treatment of such cases must be highly individualized The common aim, however, is complete separation of the urinary and intestinal tracts and establishment of control at both outlets Recent experience has demonstrated the advantages of combined abdomino perineal "pull-through" type operation Preliminary colostomy may be desirable in certain cases

ACKNOWLEDGEMENTS

I wish to thank Miss Patricia O'Neill for her skill and accuracy in illustrating the conditions present in these cases Without these drawings, and without the photographic reproductions by Mr Robert Sage, the paper would be unintelligible, I fear

P O Box 28, Dallas 1, Texas

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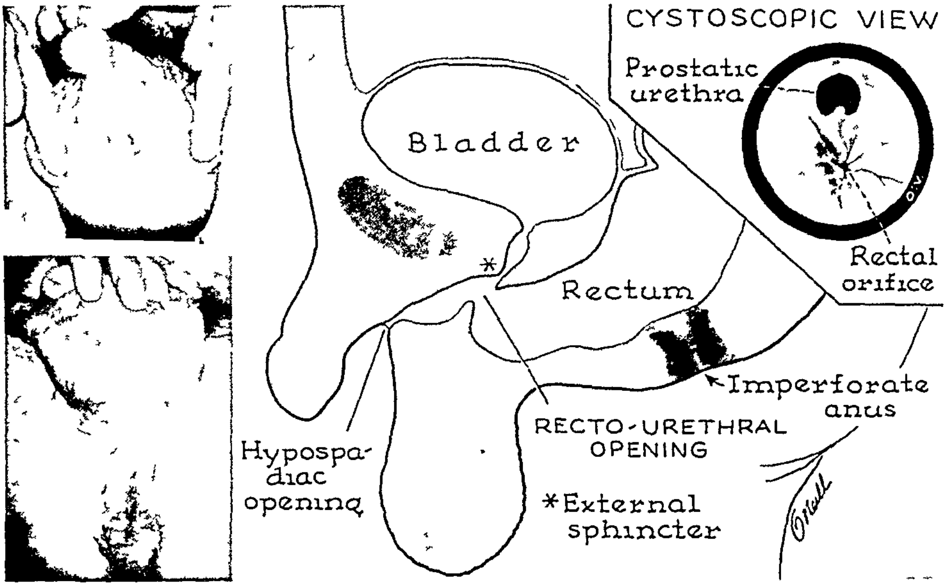

FIG 13 Case 6 At left (above) penoscrotal hypospadias through which all excreta passed (Below), imperforate anus. Diagram shows abnormal communication.

excreta through the hypospadiac opening shown in figure 13. He was continent of both urine and feces. The remarkably normal appearance of the upper urinary tract is shown in figure 14, *A*. The urethrogram (fig. 14, *B*) demonstrates the separate openings of the prostatic urethra and the bowel into the bulbous urethra. No operation was recommended in this case as I doubted my ability to improve the satisfactory functional result he had enjoyed for 41 years.

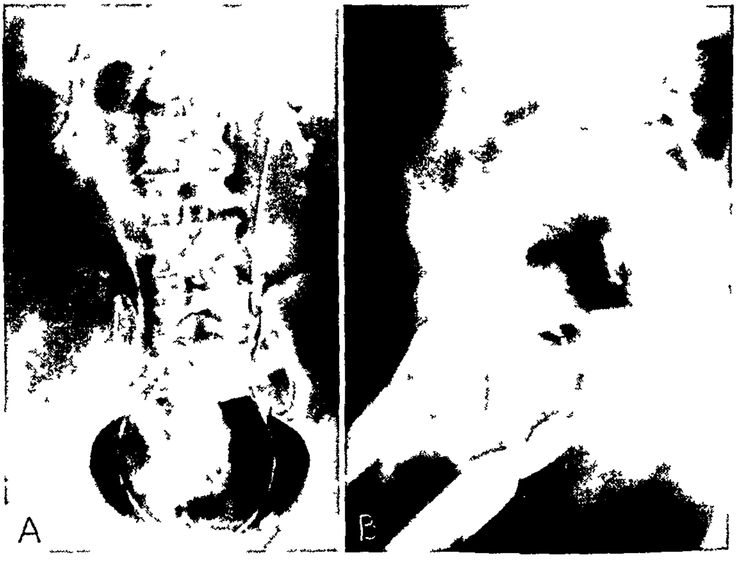

FIG 14 Case 6 *A*, normal retrograde pyelogram *B*, urethrogram through hypospadiac meatus showing prostatic urethra and rectal aperture.

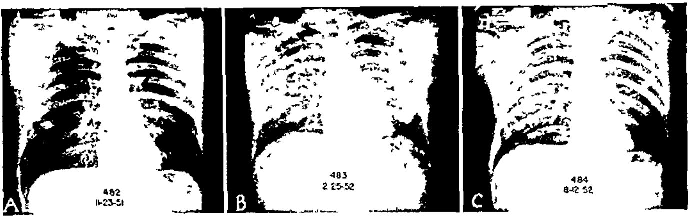

FIG. 1. *A*, normal x-ray film of chest, November 23, 1951. *B*, extensive miliary involvement of both lung fields, February 25, 1952. *C*, August 12, 1952, taken after completion of stilbamadine therapy. Note degree of clearing that has taken place.

This profuse green-yellow discharge was different from the purulent secretion of severe prostatitis. A similar secretion is described by Bunge and Harness in their case. There were no other positive physical findings. The skin was clear and lungs were negative on examination. Admission x-ray film of chest was normal (fig. 1, *A*). Excretory urogram was normal. Serology was negative. Acid phosphatase 0.0, S.J.R. units, blood urea nitrogen 18. Urinalysis revealed a trace of albumin and numerous white blood cells and 5–6 red blood cells per high power field. An electrocardiogram was normal. The patient was placed on a regimen of gantrisin 1.0 gm. every 6 hours and prostatic massage twice a week for 2 weeks. On December 11, 1951 an area of fluctation was noted in the prostate at the base of the gland and concomitantly he became considerably more comfortable. Shortly after this an ulcerated, vesicular eruption developed over the face, arms, back and left foot. On December 26, 1951 he was seen by the consultant in dermatology who made a tentative diagnosis of furunculosis. On December 27, 1951 the prostate was exposed through a perineal approach and a large abscess involving most of the gland was incised and drained. Cultures from the prostate and the skin lesion produced Blastomyces dermatitides thus first establishing the diagnosis. Further studies were initiated with these findings: Skin sensitivity test with both autogenous and stock vaccine employing 0.1 cc of 1/10,000 dilution produced no reaction; complement fixation (performed by Department of Mycology, Duke University Hospital) positive 1:4; in vitro sensitivity tests to undecylenic acid demonstrated complete inhibition in less than 3 micrograms per mililiter with good growth in the controls. X-ray films of the lungs January 4, 1952 revealed a diffuse punctate, miliary nodulation throughout both lung fields. He was given a trial of potassium iodide during which the skin lesions became worse, and bilateral epididymitis developed, therefore potassium iodide was discontinued and undecylenic acid 13.20 gm. daily in four divided doses was administered beginning January 11, 1952. This with gantrisin 1.0 gm. 4 times daily, supportive therapy in the form of blood transfusions, vitamins and a nourishing diet was his treatment for several months. An x-ray taken February 25, 1952 is shown in figure 1, *B*. During this time he gradually improved and then began to relapse with recurrence of the prostatic abscess. Therefore undecylenic acid was discontinued on April 5, 1952 and aureomycin 3 gm. daily as recommened by McVay and Carroll[4] was instituted. At this time x-ray examination of

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BLASTOMYCOSIS OF THE PROSTATE WITH MILIARY DISSEMINATION TREATED BY STILBAMIDINE

ALBERT H. BURR AND THOMAS R. HUFFINES

From the Urological Section, Veterans Administration Hospital, Oteen, N. C.

North American blastomycosis was first described by Gilchrist in 1894.[1] It is caused by infection with Blastomyces dermatitides, a fungus which on Sabourauds medium at room temperature grows as a white mould with characteristic mycelia.[2, 3] The portal of entry is not known. It is generally believed that the fungus enters the body via the respiratory tract or through an abraided skin area.[4, 8] Involvement of prostate occurs, though rarely, in the systemic form of the disease. Moore and Halpern[5] after a review of the literature found 12 instances of prostatic involvement, all of them part of disseminated disease. They add 2 cases of blastomycosis of the prostate both with lung lesions. In both of these cases the presenting symptoms were those of vesical neck obstruction. In one case, the cutaneous lesions followed four weeks of prostatic massage. Bunge and Harness[6] add 1 case of prostatic involvement accompanied by pulmonary blastomycosis later developing cutaneous lesions, though no prostatic massage was employed. Botvinick[7] reports a case presenting first cutaneous lesions, then one year later a prostatic abscess and roentgenologic evidence of pulmonary disease. Blastomyces dermatitides was obtained from the prostatic secretion. Schwartz and Baum[8] reviewed 58 cases of blastomycosis; twenty-two from Cincinnati and thirty-six from files of the Armed Forces Institute of Pathology. They found 6 patients with prostatic involvement. These were secondary to systemic blastomycosis primarily with pulmonary involvement. This is an excellent review. The purpose of this presentation is twofold: 1) to record the following additional case of prostatic blastomycosis which is apparently unique in that the primary lesion was in the prostate without demonstrable systemic or cutaneous disease on admission; and 2) to report the favorable response in a patient with severe miliary blastomycosis to stilbamidine.

CASE REPORT

A 55 year old white male carpenter recently returned from Eastern, N. C. (an endemic area according to Martin and Smith[2]) was admitted to the urologic section November 22, 1951 with symptoms of vesical neck obstruction. Examination revealed a firm, enlarged prostate gland, grade 3, which was tender. Prostatic secretion after massage was green-yellow in color, copious in amount and was a solid mass of pus cells on microscopic examination of the wet drop.

Accepted for publication April 29, 1953.

[1] Gilchrist, T. C.: J. Cutan. and Genito-Urin. Dis., **12:** 496, 1894.
[2] Martin, D. S., and Smith, D. T.: Am. Rev. Tuberc., **39:** 275–304, 1939.
[3] Martin, D. S. and Smith, D. T.: J. Lab. and Clin. Med., **21:** 1289–1296, 1936.
[4] McVay, L. V., Jr. and Carroll, D. S.: Am. J. Med., **12:** 289–301, 1952.
[5] Moore, M. and Halpern, L. K.: J. Urol., **60:** 612–622, 1948.
[6] Bunge, R. G. and Harness, W. N.: J. Urol., **66:** 263–264, 1951.
[7] Botvinick, I.: A. M. A. Arch. Derm. Syph., **62:** 936–037, 1950.
[8] Schwartz, Jan and Baum, G. L.: Am. J. Clin. Pathol., **21:** 999–1029, 1951.

inserted into the prostatic cavity This initial focus gave no further trouble and thereafter the prostate remained barely palpable and free of infection However, the patient continued to decline and aureomycin was stopped June 8, 1952 when stilbamidine became available to us At this time, the patient was moribund in appearance with a daily fever spiking to 101F, bedfast and unable to feed himself Weekly blood counts revealed persistent leukocytosis averaging 15,000 to 20,000 and sedimentation rate performed once a month ranged from 26 to 30 The increased spinal fluid protein has been noted above leading to the suspicion at least, of central nervous system involvement and to support this there were personality changes Beginning June 9, 1952 150 mg of stilbamidine in 500 cc of normal saline was administered intravenously daily for 17 days A second course was given starting July 17, 1952 aggregating a total of 4 8 gm A rest period between courses was observed Two weeks after the initial dose, the skin lesions were healed He began a gradual but definite general improvement, with increase in strength and well being, and mental clearing accompanied by progressive decrease in the miliary nodularity in chest films The film dated August 12, 1952 showed only faint interstitial infiltration left upper lobe and right mid lung field (fig 1, *C*) He became afebrile, the leukocytosis declined to 10,000 on August 1, 1952 and sedimentation rate was 22 on August 12, 1952 The rather severe conjunctivitis failed to respond to treatment with aureomycin ointment and gantrisin eye drops, but gradually subsided on treatment with cortisone eye drops and stilbamidine The epididymitis persisted unchanged and was not treated surgically since it would entail danger of further miliary spread The patient was discharged but was readmitted on October 7, 1952 with severe epididymo-orchitis, right The left epididymitis was essentially unchanged The difficult decision to perform bilateral epididymo orchiectomy was established This surgery was "covered" with another course of stilbamidine Operation performed on October 24, 1952 first ligating both cords to prevent spread during manipulation Postoperative course has been uneventful There has been no evidence of any reactivation of the disease Pathological examination of the removed organs by Dr E D Peasley confirmed the diagnosis (fig 2)

The patient returned for follow up examination November 23, 1953 No evidence was found of activity of the blastomycosis X-rays of the lungs were normal The blood count was normal, sedimentation rate normal No evidence was present of activity of the eye lesion or of the prostatic lesion, and the skin revealed no evidence of activity

COMMENT

There are several pertinent factors in this case which justify emphasis 1) The only similar case found after a rather careful investigation of the literature is that reported by Moore and Halpern [5] 2) The rapid, severe miliary spread following or coincidental with prostatic massage 3) The apparently excellent response to stilbamidine after adequate trial with the common and less common therapeutic agents recommended for the treatment of this lethal disease This encouraging response is more impressive when it is noted that in addition to the type of disease, that is, combined systemic and cutaneous, the skin test was negative and complement fixation positive, a nearly hopeless condition according to the immunologic studies of Smith.[9]

Blastomycosis is not a rare disease. Since 1942, nine patients with this infection have been treated at these hospitals and four are currently under treatment. These 13 cases represent blastomycosis confirmed by culture, surgical specimens or autopsy. They will be analyzed in greater detail in the paper mentioned below. Only two of these thirteen individuals represent the purely cutaneous form of the disease. Autopsy material is available in 3 cases, two of which present renal involvement by blastomycosis, but no other genito-urinary infection with this fungus.

The results of undecylenic acid in the treatment of fungus diseases will be presented elsewhere by the Thoracic Surgical Service, Oteen Division. A comprehensive study of stilbamidine and other aromatic diamidines, their pharmacology, mode of action and therapeutic potentialities is presented by Schoenbach and Greenspan.[10] Case reports of clinical use have been made by Schoenbach, Miller, Ginsberg and Long[11] and Schoenbach, Miller and Long.[12] These authors were the first to use this drug in the treatment of blastomycosis. Stilbamidine should be administered only in a hospital where the patient can be followed with hepatic and renal function studies, serial x-ray examinations, urinalyses, blood counts and neurological examination. All of these were carried out in this patient but are not recorded in detail since no pertinent findings were encountered other than noted in the case report. It is a potent drug and instances of trigeminal neuropathy and kidney and liver injury and death have been collected and recorded in the articles by Schoenbach et al. When fresh powder unexposed to sunlight or air has been employed serious hepatic or renal damage has not been encountered. The neuropathy is a late and unexplained complication.

CONCLUSIONS

A case of severe, miliary blastomycosis following or co-incidental with prostatic massage of a primarily involved prostate resulting in demonstrable involvement of lungs (severe); skin; epididymides, bilateral; and probably of the right eye and central nervous system is presented.

Encouraging results, following treatment with stilbamidine after adequate trial with the common and uncommon therapeutic agents recommended for the treatment of this highly fatal disease are recorded.

Further trial of stilbamidine is recommended.

Blastomycosis is not a rare disease; thirteen proven cases have been encountered at these hospitals during the past ten years.

The authors express their gratitude to the staff of the Medical Service of this hospital who assumed the care of this patient after his second operation and administered the stilbamidine.

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[9] Smith, D. T.: Ann. Int. Med., **31:** 463–469, 1949.

[10] Schoenbach, E. B. and Greenspan, E. M.: Medicine, **27:** 327–377, 1948.

[11] Schoenbach, E. B., and others: J. A. M. A., **146:** 1317–1318, 1951.

[12] Schoenbach, E. B., Miller, J. M., and Long, P. H.: Ann. Int. M., **37:** 31–47, 1952.

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PERSISTENT ANTERIOR LOBE OF THE PROSTATE GLAND

OSWALD S LOWSLEY AND ALEJANDRO PEREZ VENERO

From the Oswald Swinney Lowsley Foundation, Inc, St Clare's Hospital, New York, N Y and the Clinica San Fernando, Panama, R P

Studies of the embryology of the prostate gland, made by the senior author in 1912, revealed the fact that the human prostate gland begins its development in the third month of intra uterine life, from five foci which later form the five lobes of the gland, namely, the anterior, posterior, middle, and right and left lateral lobes In this communication, we are concerned particularly with the anterior lobe

Cases of disease of the anterior lobe are so rare that the authors deem it advisable to call the attention of the profession to the fact that such lesions do occur occasionally and require treatment

EMBRYOLOGICAL CONSIDERATIONS

The anterior lobe of the prostate gland begins its development simultaneously with the other lobes, being formed from tubules originating from the ventral, or anterior, wall of the posterior urethra together with their surrounding stroma At first relatively large and multi-branched, and of equal importance to the tubules of the other lobes, they gradually contract, and by the twenty second week appear to have lost most of their branches Thereafter, they shrink into increasing insignificance so that at birth the anterior lobe tubules show no lumina and appear as small, solid epithelial outgrowths

On rare occasions, however, the anterior lobe tubules persist into adult life In one case observed by the senior author, the prostate of a 17-year-old boy, who died from pneumonia, showed anterior lobe tubules fully developed and filled with secretion, just as were the tubules of the other lobes

Over a period of 44 years of study of, and surgical experience with, the prostate gland, the senior author has observed only 18 cases of persistence of the anterior lobe The material studied has consisted of embryological, anatomical, and surgical specimens, and these have numbered in the thousands

CLINICAL ASPECTS

Most of the persistent anterior prostatic lobes have consisted of small (pea-sized) intrusions from the ventral aspect of the vesical sphincter, and have been discovered at routine cystoscopy or at autopsy, having caused no untoward symptoms

However, more serious results are observed on occasion The lobe may become subject to disease—almost always adenomatous hypertrophy—and may then cause serious obstruction to urination

When there is an enlargement of the anterior lobe, it is usually a solitary enlargement—this lobe rarely participating in a general enlargement of the prostate gland

Read at annual meeting, American Urological Association, St Louis, Mo May 12, 1953

One anterior lobe intrusion was seen by the senior author together with Leon Howard, of Denver, and in a recent personal communication he stated that he had seen only one other in 45 years of "looking into bladders." In both of these cases, the lesion had the appearance and feel of malignancy. The first patient was lost track of and the pathological diagnosis is unknown; in the second case, the resected tissue showed no evidence of malignancy.

More recently, 2 cases with adenomatous hypertrophy have been observed. Both were treated by operation, and are described below.

CASE OF PERSISTENT ANTERIOR LOBE WITH HYPERTROPHY TREATED BY SUPRAPUBIC ENUCLEATION

In a case of the junior author, seen at the Clínica San Fernando, in Panama, an anterior lobe caused complete obstruction to urination in a comparatively young man (aged 30 years), necessitating removal by a suprapubic operation.

A. A., aged 30 years, was admitted to the Clínica San Fernando on August 20, 1952, complaining of recurrent episodes of marked difficulty in urinating. He stated that, so far as he could remember, he had never been able to void freely, always requiring several minutes of straining to initiate the act, with continued difficulty throughout the act. This difficulty would be more marked at some times than at others, and when increased, he would also feel tired and nervous. There had been no nocturia or hematuria. He was married, had three children, and the sexual act was entirely satisfactory. Five years previously, he had been advised to have a cystoscopic examination but had refused because of fear of instrumentation.

Physical examination revealed a small urethral meatus but was otherwise negative. The prostate per rectum was of average size and consistency, and symmetrical in outline. The secretion showed only a few pus cells. However, on asking the patient to void, a marked difficulty was observed, about 5 minutes being required to initiate the act. The urinary stream was of small caliber with weak force. The laboratory findings were all within normal limits. The blood pressure was 110/80.

Under local anesthesia, and following a meatotomy, cystoscopic examination and bilateral pyelography was performed. A solid tumor mass was found at the anterior portion of the bladder neck; cystoscopically, this resembled a middle lobe prostatic hypertrophy, grade III, in an inverted position. The bladder wall showed moderate coarse trabeculations but there was no residual urine. Inspection of the bladder neck with the retrograde lens showed the tumor mass to be attached to the anterior lip of the bladder orifice from about 10 o'clock to 2 o'clock, protruding into the lumen and extending more intravesically than intraurethrally. The upper urinary tract was anatomically and functionally within normal limits, and the urine from each kidney was negative on stained smear and culture.

A diagnosis of "hypertrophy of a persistent anterior lobe of the prostate with urinary obstruction" was made and operation advised. A consultation was held with other urologists in Panama and with the senior author, who was visiting

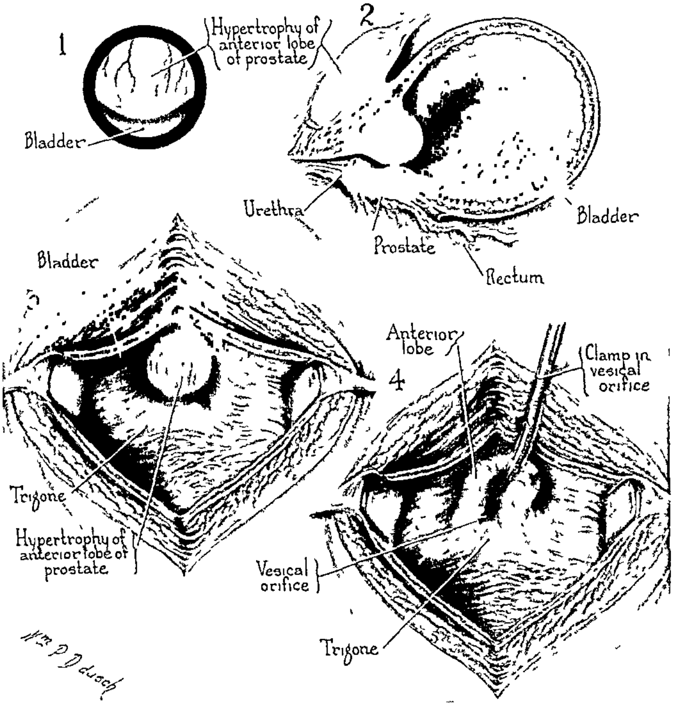

FIG 1 Adenomatous hypertrophy of persistent anterior lobe of prostate removed by . ⁞ this case, was more intravesical than intra-urethral . . . en through the cystoscope *2*, Sagittal view showing posure of hypertrophy *4*, Clamp in vesical orifice, showing extent of hypertrophy of anterior lobe

there, and the diagnosis was confirmed by all. It was suggested that the mass might be removed by either transurethral resection or suprapubically, but the transvesical approach was chosen by the junior author as the mass seemed to be more intravesical than intraurethral.

On September 3, under spinal anesthesia, and without preoperative catheter drainage, operation was performed by the junior author. Using a conventional midline incision, the bladder was opened and the tumor easily enucleated after incising the mucous membrane over it. The mucous membrane was then closed with interrupted sutures, and bleeding controlled by traction for 24 hours on a Foley catheter with a large bag. The prevesical space was drained and a suprapubic tube was left to drain the bladder (fig 1).

A blood transfusion of 500 cc was given during the operation, and the immediate postoperative condition was excellent.

The pathological report described a solid mass of grayish tissue, semi-ovoid in shape, with a smooth convex and a rough concave surface, weighing 9 gm. The microscopic diagnosis was: "Benign cystic adenoma of the anterior lobe of the prostate."

Postoperatively, there was very slight bleeding for the first 48 hours and none thereafter. On the eighth day, the suprapubic tube and prevesical space drains were removed and the wound allowed to heal. The Foley catheter was removed on the sixteenth day, and the patient was able to void freely with no leakage from the wound. Two days later, he developed a temperature of 101F but there was no evidence of fluid or pus in the prevesical space. The indwelling catheter was replaced and mixed antibiotics were given, as the urine showed many pus cells and a mixed gram-negative bacilli and gram-positive streptococci flora. The temperature subsided 2 days later, and in another 2 days the catheter was removed but the antibiotics were continued. He was discharged on the twenty-fifth postoperative day, free of fever, feeling well, voiding freely, and with negative urine.

One month after his discharge, a 27F sound was passed with ease. He has been followed for 6 months and now voids freely, has excellent sphincteric control, and states that he never felt better in his life.

CASE TREATED BY TRANSURETHRAL RESECTION

C. G., aged 62 years, was admitted to St. Clare's Hospital on November 9, 1952 because of urinary frequency, urgency, dribbling, and dysuria.

Eight years previously, he had had a transurethral resection for adenomatous hypertrophy of the prostate, but there had been persistence of the urinary symptoms. Otherwise, his past history was uneventful, save for an appendectomy and a bilateral epididymectomy for chronic epididymitis 5 years earlier.

Physical examination was negative except for absence of the epididymides. The blood pressure was 150/90. The laboratory findings were within normal limits. The blood urea nitrogen was 15.1.

Cystoscopic examination revealed a completely satisfactory removal of the middle and lateral portions of the prostate gland. However, there was a mass on the roof of the vesical orifice, about the size of the end of one's thumb. This was diagnosed as a persistent anterior lobe of the prostate that had become hypertrophied.

On November 10, under spinal anesthesia, and without preliminary catheter drainage, transurethral resection of this mass was done. With the Kirwin resectoscope, the projecting areas of tissue were carefully removed and sent to the laboratory for examination (fig. 2).

The pathological report was as follows: "Gross: Specimen consists of 9 pieces of prostatic tissue weighing altogether 4 gm. The largest of these measures 1.8 by .9 by .5 cm. and the smallest 6 by 5 mm. They are of moderate consistency. Microscopic: The glands are, for the most part, regular, but a few show multi-

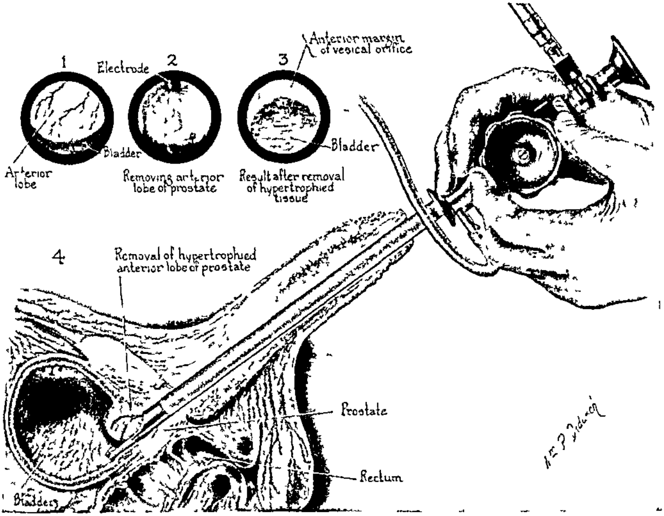
1
Electrode
2
3
Anterior margin of vesical orifice
Bladder
Anterior lobe
Removing anterior lobe of prostate
Result after removal of hypertrophied tissue
Bladder
4
Removal of hypertrophied anterior lobe of prostate
Prostate
Rectum
Bladder

FIG. 2. Removal of hypertrophied anterior lobe with Kirwin resectoscope. *1*, Condition as seen through resectoscope *2*, Excursion of loop in removing lobe *3*, Result after removal of hypertrophied mass *4*, Sagittal section showing removal of hypertrophied anterior lobe with resectoscope

layering and infolding of the epithelium. In the region of the urethra there are collections of lymphocytes. Diagnosis: Prostate showing moderate glandular hyperplasia and moderate chronic inflammation."

Convalescence was satisfactory, and the patient was discharged on the fifteenth postoperative day in very good condition.

Subsequently, a 28F sound was passed on two occasions. He is now entirely free from the symptoms which brought him in for the second operation. There is no residual urine, and his urine is clear.

SUMMARY AND CONCLUSIONS

The anterior lobe of the prostate gland is usually only of academic interest, because by the time the child is born it has, in most cases, shrunken to insignificance.

In a few instances it may persist and become subject to disease. The lesions thus far met with in the senior author's experience, numbering 18, have always been adenomatous hypertrophy—with the possible exception of one case, which was believed, but not proven, to be carcinoma.

An enlargement of the anterior lobe manifests itself by causing obstruction to urination, very much in the same manner as does enlargement of the subcervical group of tubules. This interference with micturition may vary from slowness in starting the stream, to incomplete emptying of the bladder with a considerable amount of residual urine. In fact, one of our patients stated that he never in his entire life knew what it was to void with comfort until after his anterior lobe had been removed.

Attention is called to this condition because it is quite possible to overlook the lesion which may be entirely unsuspected as the cause of obstruction, coming, as it does, from the ventral aspect of the vesical orifice.

The treatment consists in removal of the obstructing mass. This may be done either by open operation with enucleation, as in one of the cases described here, or by transurethral resection, which was done in another of our patients.

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MALIGNANT TESTIS TUMOR, CRYPTORCHIDISM AND POLYORCHIDISM IN A PSEUDOHERMAPHRODITE

JACOB TAUB

From the Department of Pathology, Westchester Square Hospital, Bronx, N Y

Approximately 66 cases of malignant testicular tumor in pseudohermaphrodites have been reported in the literature The first such case was described by W L Gruber in 1859 Neugebauer[1] in his monograph discussed 12 cases reported between 1859 and 1907 Gilbert and Hamilton[2] in analyzing 345 tumors of intra-abdominal testes found 11 per cent or 38 of them to be associated with congenital defects classifying them as pseudohermaphrodites with the defects ranging from hypospadias to rudimentary portions of the female reproductive tract In many cases the pseudohermaphroditism was not suspected until exploratory laparotomy had been done In 1940 J B Gilbert[3] reviewed the literature from 1859 and reported on 61 cases including one of his own Up to the present time only five additional cases [4, 5, 6, 7, 8] have been reported

The sex of an individual is zygotically determined as soon as union of ovum and sperm occurs, but it is not until the sixth or seventh week of embryonic life that the gonads in the genital folds differentiate into either the ovary or the testis In the male embryo the wolffian body and duct are stimulated into the development of a vas deferens, seminal vesicle and an epididymis At the same time the mullerian structures whose purpose it is to form a uterovaginal canal with ovarian development, remain as vestiges

A pseudohermaphrodite is a person in whom the gonads of only one sex are present in association with the external and/or internal genitalia of the opposite sex According to Young,[9] the probable explanation for intersex is a disturbance of the chromosome formula, but in any one case of pseudohermaphroditism where the predominating gonad is the testis, repression of the mullerian elements, namely the uterus, tubes and vagina depends on the amount of interstitial tissue present in the undescended testicle

The incidence of hermaphroditism in cryptorchids is 1 per cent Tumors are 20 times more frequent in undescended than in fully descended testicles, and it is estimated that 10 per cent to 15 per cent of all testicular tumors are found in the undescended testes[10] The intra abdominal adult testis is usually atrophic and aspermic Why malignancy is particularly prone to develop under such

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[1] Neugebauer, F L v Hermaphroditismus beim Menschen Leipzig W Klinkhardt, 1908 748 pp

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[3] Gilbert, J B J Urol, 48 665-772 1942

[4] Wenner, R and Scheidegger, S Monatschr f Geburtsh u Gynak 115 57 66, 1943

[5] Lacerda Jr Rev Brasil de Cir, 12 565-574, 1943

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[8] Galucci C An paulist med e cir, 59 359-372, April 1950

[9] Young Hugh H Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases Baltimore Williams and Wilkins, 1937 p 50

[10] Haines, J S and Grabstald, H Arch Surg, 60: 857-860, 1950

conditions is difficult to understand. It is possible that the higher intra-abdominal temperature may be contributory. Also the anomalous descent of the gonad may coincide with an anomalous development of its parenchyma. Pituitary imbalance and increased hormonal secretion may also play a part.[11]

The testis is composed of totipotent sex cells and it can produce a large variety of tumors derived from all three layers of germinal epithelium. More commonly the tumors are unicellular due to a one-sided development with repression of the other germ layers. However, approximately 25 per cent of testicular tumors are composed of embryonal structures more or less derived from all three germ layers and these are designated as teratocarcinoma. Pick[12] has described a benign tumor found in one of the undescended gonads of an hermaphrodite as arising from seminiferous epithelium and has called it the adenoma tubulare. The tumor most commonly found in the undescended testis is the seminoma. It is believed to arise from asexual gonadal tissue, is unicellular and composed of large, round or polyhedral cells of embryonal type lying in a stroma richly infiltrated with lymphocytes. Other more malignant varieties sometimes including the seminoma are loosely classified as embryonal carcinoma. Choriocarcinomas also arise in the testicle but their exact origin is not clear. The atrophic or cryptorchid testis frequently undergoes marked hyperplasia of the interstitial tissue to form tumors of moderate dimensions, the so-called interstitial cell adenoma.

The following case shows all the aforementioned varieties of tumor formation.

CASE REPORT

A man, aged 18, was admitted to the hospital with a complaint of pain in the right lower quadrant of 24 hours' duration. He had tenderness and rigidity and leukocytosis. A preoperative diagnosis of acute appendicitis was made and the patient was prepared for an abdominal laparotomy. In view of the surgical-pathological findings it is well to point out that the patient was a normal, well developed male with male distribution of hair, fat and bone structure. He possessed the external features of a well developed adult. His penis was of normal size and included the glans with a complete urethra. There was no evidence of hypospadias and the perineum was intact. The only abnormality noted was the absence of both testes from the scrotal pouch. The patient stated that in childhood he had been treated with injections for undescended testicles. Four years before the present admission he had been operated on for a right inguinal hernia at which time no testis was found in the inguinal canal. Despite his cryptorchidism the patient's physical and psychological makeup was definitely masculine.

The abdomen was opened through a right rectus incision, but because of the large amount of blood that gushed up into the wound from the abdominal cavity, this incision was closed and a larger exploratory opening was made in the midline. Approximately 500 cc of clotted blood was found in the peritoneal cavity. This was removed and a large, freely movable, globular tumor measuring 10 by 7 by 6 cm. presented itself (specimen A, figs. 1 and 2). The base of

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[11] Twombly, G. H.: Are testis tumors the result of pituitary imbalance? Proceed. N. Y. Pathological Soc., 1950–1951, pp. 38–41.

[12] Anderson, W. A. D.: Pathology. St. Louis: C. V. Mosby Co., 1948, p. 1118.

FIG. 1. Specimens removed separately at operation and are arranged haphazardly. Uterus, *C* [illegible] t undescended testis, *B*, [illegible] s, *E*. Numbers on supern [illegible] na. *2*, Tubular adenoma and adenocarcinoma. *3*, Embryonal carcinoma. *4*, Choriocarcinoma.

this tumor was attached by a narrow pedicle measuring 5 by 1.5 cm. to a structure on the posterior abdominal wall in the right pelvis which resembled a broad ligament. The upper third of this tumor had undergone hemorrhagic necrosis and infarction. There was a tear along the free border of the infarcted area and this accounted for the intra-abdominal bleeding.

Further exploration of the abdomen revealed remarkable abnormalities of the sexual apparatus. Lying in the pelvis in the midline was a small narrow rudimentary uterus (specimen C, figs. 1 and 3) measuring 7 by 2 by 1.5 cm. including both fallopian tubes which were well formed and terminated in the fimbriae. Both broad ligaments were present and as mentioned above, the tumor appeared to arise from the right broad ligament. The right fallopian tube appeared to

FIG. 2. Malignant supernumerary testis. A_1, area showing seminoma. A_2, area showing atrophic seminiferous tubules, rete testis and interstitial cell adenoma.

partly embrace the tumor at its base. Within the left broad ligament just below the left fallopian tube and medial to the fimbriated end was a small ovoid body measuring 2 by 1.5 by 1.5 cm. On gross section this had the consistency and yellowish appearance of testicular tissue but was only half the size of the normal testis (specimen E, fig. 1). No epididymis or vas deferens was attached. Microscopically this tissue consisted of rete testis, inactive and atrophic seminiferous tubules, and there was no evidence of spermatogenesis. The tubular basement was thickened and hyalinized and the interstitial connective tissue was increased (fig. 4, *D*). Several of the tubules contained small round amorphous concretions similar to the corpora amylacea seen in the prostate gland. The histological appearance was characteristic of an atrophic undescended testis.

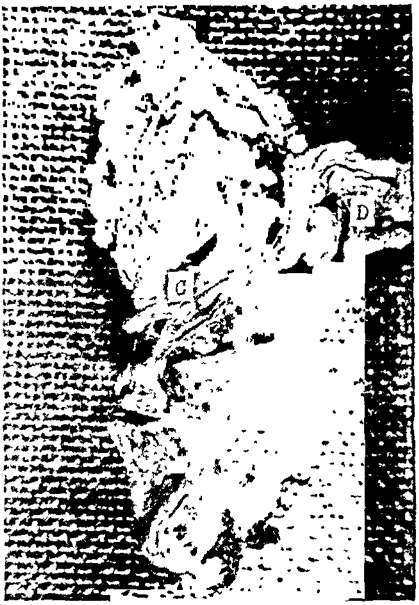

FIG. 3. Rudimentary uterus with left fallopian tube, *D*, attached.

To the far right of the large tumor and not related or attached to it was an oblong retroperitoneal mass measuring 6 by 2.5 by 1.5 cm. This mass lay in the right abdominal gutter at the pelvic brim. It had undergone an almost complete hemorrhagic necrosis and infarction but this in no way had contributed to the intra-abdominal bleeding. The lower end of this mass was continuous with several loops of tubular tissue which could be palpated for a short distance and then disappeared into the deep tissues of the pelvis. Histologically these tubular structures were identified as vas deferens (fig. 4, *E*) and epididymis (fig. 4, *F*). It was believed that this retroperitoneal mass was a right undescended testis (specimen B and F, fig. 1). However it contained no seminiferous tissue due not only to the extensive hemorrhagic necrosis but to the infiltration by syncytial masses of polyhedral trophoblasts. The histological picture was characteristic of choriocarcinoma (fig. 4, *B* and *C*) and this was confirmed when a Friedman pregnancy test done on the fifth postoperative day was reported back as strongly positive.

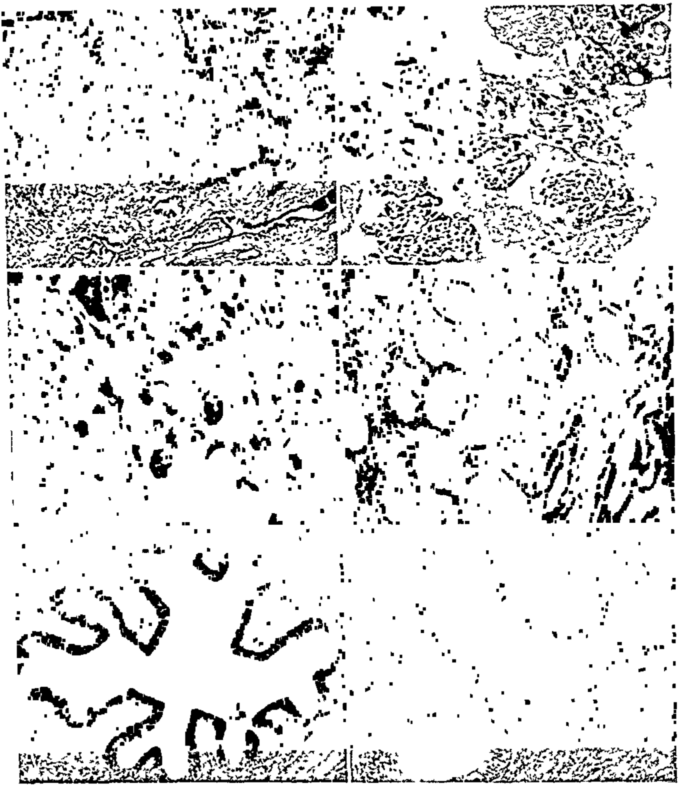

FIG 1 *A*, low power. Rete testis and atrophic seminiferous tubules of supernumerary testis *B*, low power. Choriocarcinoma of right undescended testis. *C*, high power. Choriocarcinoma of right testis. *D*, low power. Rete testis and atrophic seminiferous tubules of left undescended testis *E*, low power Vas deferens of right testis *F*, low power Epididymis of right testis

All the aforementioned tissues, including the right and left undescended testes, the pedunculated infarcted tumor, the uterus and fallopian tubes were dissected away and removed. The endometrial cavity which was 1 cm. in diameter was probed from above but no connection between the uterine canal and the perineum or rectum was established. The probe was stopped at a blind point deep in the pelvis about .5 cm. from the perineum. Microscopic sections through the fallopian tubes showed typical villiform structures (fig. 5, *B*). Sections through the uterus showed proliferative endometrial glands imbedded in smooth muscle (fig. 5, *A*).

The large tumor presented features of unusual interest. The outer third of the scrotal pouch.[17, 18, 19] Not all have vasa deferentia. In one case the diagnosis was made on a small remnant of epididymis and it was assumed that complete atrophy of the testis connected with this epididymis had followed. Ranson described a case[20] in which a vas deferens containing spermatozoa was attached to a small fatty mass which contained no seminal tissue.

In our case the evidence for a right testis is established by the presence of a right vas deferens and epididymis. No testicular tissue was demonstrable because of extensive infarction and tumor transformation of the mass attached to these appendages. However, the nature of the malignancy, i.e. choriocarcinoma, implies a prior existence of a testis since this type of tumor has a particular affinity for that organ. The left gonad had no vas or epididymis but was easily identified as testis by microscopic examination. The large tumor is considered a supernumerary testis on the basis of the atrophic seminal tubules and rete testis found in the periphery, the interstitial cell hyperplasia and the tubular adenoma. Despite its proximity to the right testis there was no connection between the two.

Cryptorchidism, pseudohermaphroditism, teratocarcinoma or polygonadism per se have been frequently reported in the literature but an exhaustive review fails to reveal any reports in which these conditions existed collectively or concomitantly in one individual. Another unusual feature was the co-existence of several varieties of tumor tissue in the supernumerary testis. It was therefore felt that this case report warranted publication. I am indebted to Dr. Ignatius M. Bopp, attending physician and Dr. Henry Wahn, Jr., attending surgeon for permission to publish details of this case.

2475 St. Raymond Ave., Bronx 61, N. Y.

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[18] Smith, P. G., Evans, A. T. and Suder, G. L.: J. Urol., **64:** 515-517, 1950.
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ACUTE GRANULOMATOUS ORCHIDITIS

WILLIAM DREYFUSS

From the Department of Urology, Huron Road Hospital, Cleveland, Ohio

Granulomatous orchiditis is a subject of indefinite etiology The literature is scanty and the reported cases represent the chronic phase of the disease Apparently the final histological picture can be the end result of various etiological factors The early stages of acute granulomatous orchiditis should be more revealing and therefore the following case is being presented

CASE REPORT

Mr W I , aged 29, had a family and past history that was noncontributory He became ill August 24, 1951 with a "chest cold " On August 26, a diagnosis of bronchopneumonia was made He was treated by 1,150,000 units of penicillin and bed rest until September 4 On the evening of September 4, he complained of constant ache in both testicles The pain radiated upwards into both groins He was given 32 capsules (250 mg) of terramycin His pain continued even after aureomycin was substituted which he took until September 24 On this day he was seen in consultation because of a suspicion of a testicular tumor and he was immediately hospitalized

Physical examination was negative except for local findings Blood pressure 130/80, pulse 80, temperature 37 7°C, respirations 18 The scrotum was not enlarged or discolored The testicles were normal in size and the patient confirmed that there was no change The right epididymis and cord were normal The vas was not thickened or tender The right testicle contained a very hard mass 7–10 mm in diameter which was tender, but not unusually so to palpation On the left side, a small area of induration that was present did not have the stony hard consistency felt on the right side It was located in the lower pole and it was difficult to decide whether it was in the testicle or epididymis The left cord and vas were normal The inguinal lymph nodes were not unusually enlarged The prostate gland felt normal Because we believed that an epididymal infection existed on the left side, no massage specimen for microscopic study was obtained

Laboratory findings Admission and all subsequent urinalyses were within normal limits Blood count hemoglobin 13 6 gm (87 7 per cent), red blood cells 4,380,000, white blood cells 12,250 The differential count was within normal limits Blood chemistry studies including alkaline and acid phosphatase and liver function tests were normal An electrocardiogram was also normal X ray examination of the chest and urinary tract showed no abnormalities

The patient was taken to the operating room September 26, 1951 with a preoperative diagnosis of possible malignant tumor of right testicle After exposure, the tunica vaginalis was split and the right testicle was examined Externally the epididymis and testicle appeared normal, except for a hard nodule, the size of a pea in the lower pole of the testicle As we were uncertain as to the possible

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malignancy of the lesion, we did not feel justified in sacrificing this organ. The tunica was split over the growth and a layer of normal testicular tissue was seen. There was no clear line of demarcation between the normal and abnormal tissue. When split, the nodule appeared hard, the center was dark and sclerotic but not calcified. The peripheral portion of the nodule appeared yellow in areas, resembling adrenal tissue. A frozen section biopsy revealed inflammatory tissue, no malignancy. The entire nodule was removed, the bleeding controlled by plain 000 catgut. The tunica albuginea was closed with interrupted sutures of the same catgut. A bottle operation was performed to prevent formation of a hydrocele and the testicle replaced and the scrotum closed. Palpation of the left testicle under anesthesia created doubt as to the location of the previously mentioned induration. In view of the unusual findings in the right testicle, it was decided to explore the left testicle. The findings on the left were similar and the treatment was the same as on the right side. Healing and postoperative course were uneventful and the patient was discharged on the eighth postoperative day. (It should be mentioned that a tourniquet was placed around the cord from the incision into the testicle till the completion of the frozen section. This was a precaution against spreading in case of malignancy.)

The specimen from the right testicle consisted of a rounded mass of reddish gray tissue measuring 1 cm. in diameter. On section there was a firm area in the central portion which was yellowish gray in color. This area measured 3 mm. in diameter.

Microscopic report (fig. 1): The section showed a small mass of tissue from the testicle with a large area of necrosis present suggesting an area of infarction. Here there were only shadows of tubular tissue with considerable hemorrhage and laking of the blood in the hemorrhagic zones. The tubular tissue basement membranes could be made out but no intact cells were seen. At the margins of the area of infarction there was an inflammatory reaction with thickening of the vessels and one medium sized vessel showed the lumen completely occluded by recent blood clot. The vessel itself showed marked thickening with proliferation by fibrous tissue in the adventitia. The regional testicular tissue showed fibrosis with absence of spermatogenesis and a thickened basement membrane was seen. The interstitial tissue was loose, very edematous and infiltrated by masses of plasma cells, lymphocytes, some large wandering cells and pus cells. Somewhat remote from the area of infarction a second blood vessel was seen showing the lumen completely filled by an organizing and secondarily canalizing blood clot.

Bacteriological studies of stained tissue were negative.

Examination of the specimen from the left testicle showed a similar picture.

Final diagnosis: Focal area of infarction of testicles with thrombosis of small vessels; regional testicular atrophy.

Because of the rarity of the pathological findings, the slides were submitted to the Armed Forces Institute of Pathology. We quote from their report: "Both testes show an essentially similar picture, which is believed to consist of focal infarction with granulomatous reaction secondary to vascular thrombosis. The arterial thrombosis is not characteristic of any vascular disease and may be traumatic."

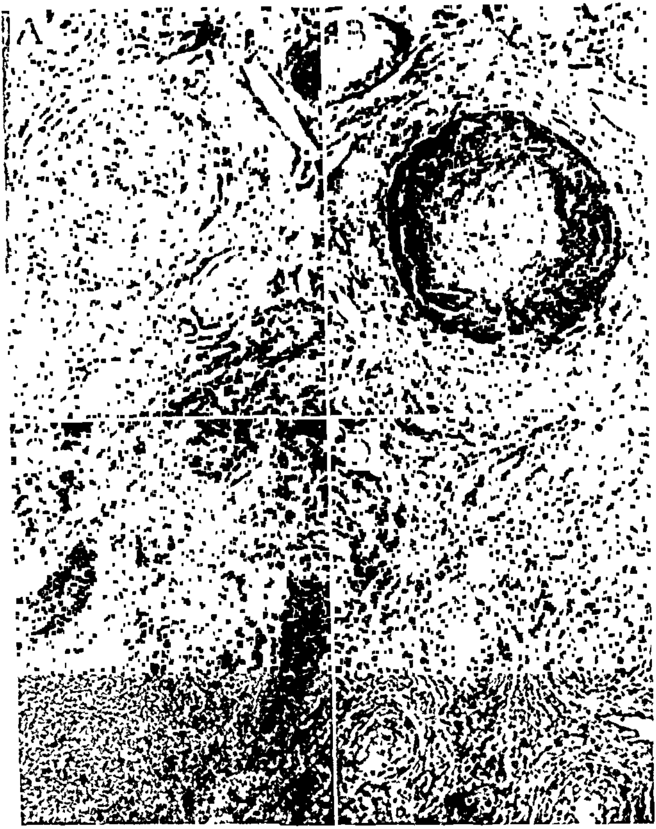

FIG 1. *A*, inflammatory thickening of arteriole with regional granulomatous orchitis. *B*, thrombosis remote from area of infarction *C*, granulomatous orchitis with infarction. *D*, interstitial granulomatous orchitis remote from area of infarction.

"The entire picture may well constitute the early stages of the so-called granulomatous orchiditis. This is a nonspecific granulomatous reaction of the testes associated with a number of diseases and believed to be due to interference with testicular blood supply. In a number of cases the testes have been removed because clinically the lesion can not be distinguished from a tumor of the testes."

The patient was re-examined on June 13, 1952, 9 months postoperative. He was in excellent general condition. He had had no testicular pain since the operation. The epididymis and cords were normal bilaterally. The right testicle was of normal size and consistency in the proximal portion. There was a dense scar in the distal part. The left testicle was normal except for a small indentation of scar tissue. Libido and potentia coeundi were preserved at the preoperative level. Sperm count on August 4, 1952: Volume 2.5 cc; count 47,700,000 sperm per cubic centimeter. Viscosity: normal. Survival rate up to 23 hours and 12 per cent abnormal forms.

DISCUSSION

Clinical characteristics, as demonstrated by the case we are reporting, were a) a sudden onset associated with a distant infectious condition; b) testicular pain present, but not dramatic; c) not influenced by treatment with antibiotics; d) development of a hard nodule in the right testicle which suggested strongly the diagnosis of malignant tumor. A similar nodule in the left side (originally misinterpreted as epididymitis).

Pathological characteristics. The microscopic picture is dominated by thrombosis of small intratesticular arteries and all other changes are secondary to this vascular phenomenon: the different stages of necrobiosis, the loose interstitial tissue, the degeneration of tubular epithelium and the thickened basal membrane, the plasma cells, lymphocytes, pus cells and wandering cells. The blood vessels show intimal proliferation, thickening of the media and thickening and infiltration (from cellular to fibrous) of the adventitia. Some vessels contain blood clot.

Had we obtained the pathological specimens 1, 2 or 12 months later, the earlier and finer changes in micropathology would not have been discernible. One can also deduce that whereas granulomatous and fibrous reaction is the most likely, abscess formation, as well as secondary involvement of the epididymis, is possible too.

The importance of this presentation rests in the fact that in this case we were able to obtain a specimen of a pathological process, which so far as we are able to determine from the literature was heretofore presented only in its chronic form. With due reservation for conclusions drawn from only one case, the histology of our case throws some light on the etiology of this rare disease, namely that we have to conclude that we are dealing with a primary damage to the vessels in the form of a thrombo-arteritis. We could not prove the presence of bacteria but the patient had intensive treatment with three different antibiotics. It is therefore undecided whether the causative factor was direct bacterial action or a toxin. There is also no answer to the question why the testicles were the only organ so involved. It is likewise open to discussion with no conclusive answer possible, whether the original affliction diagnosed as bronchopneumonia acted as a focus or whether it, as well as the testicular condition were manifestations of the same agent. The further question arises: is the thrombosis of the small vessels of the testes embolic or a primary disease of the vessels. There is absolutely nothing in the clinical and laboratory findings to support such an embolic theory. In case of embolus we would suspect a more sudden and dramatic onset. There is also no history of any trauma in this case.

The latest paper on this subject by Lee and Nettleship[1] presents advanced cases and in none of their pathological reports is there any reference to the blood vessels Some of their cases had an insidious onset with little or no pain In some the process extended clearly to the adjacent epididymis, but in others they were evidently dealing with so called ascending infections which extended from the epididymis to the testicle In all the papers which they mention as reference an "epididymo-orchitis" was described

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[1] Urol., **67**: 342–349, 1952.

We are aware that epidemic (non-mumps) orchiditis preceded by fever has been reported by the Armed Forces Careful investigation did not reveal any epidemic at the time our patient became sick

In another recent paper by Dieterle[2] mention is made of the blood vessels But here it is doubtful whether the condition he described is a granular orchiditis or an "epididymo-orchitis" in which a Sertoli cell tumor developed

We believe that we should definitely adjust our nomenclature so that it clearly reflects which pathological-anatomical entity is meant by it The term "granulomatous orchitis" should be reserved for a condition which starts in the testes proper and does not, or only rarely, extends secondarily into the epididymis The term "epididymo-orchitis" or better "epididymo orchiditis" should be reserved for any inflammation which primarily manifests itself in the epididymis and secondarily extends to the testicle Both conditions are distinctly different in etiology and should not be confused

SUMMARY

A case of acute bilateral granulomatous orchiditis is presented Clinically the picture suggested testicular tumor An attempt is made to explain this rare disease on the basis of primary affliction of the intratesticular arteries Suggestion is made to more definitive nomenclature

13944 Euclid Ave , Cleveland 12, Ohio

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[2] Schweitzer Ztschr f allg Path , 13: 265–278, 1950

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PREPENILE SCROTUM IN A DOUBLE MONSTER TERATOLOGICAL CONSIDERATIONS. THE HAZARDS OF RADIATION

THOMAS GUALTIERI AND ABRAHAM D. SEGAL
From the Coney Island Hospital, Brooklyn, N. Y.

Prepenile scrotum represents an extremely rare urological anomaly wherein the scrotum assumes a position anterior or cephalad to the penis. It is not to be confused with the condition "concealed penis" which presents a rudimentary penis concealed in the scrotal or perineal skin. The latter apparently results from a difference in the relative rate of growth of penis and scrotum, and cannot therefore be considered a true prepenile scrotum, a situation in which both organs are fully developed. In the cases reported, as well as in our own case, this anomaly is associated with multiple urogenital and extra-urogenital abnormalities. Thus in Francis' case there was a complete absence of the urinary system, an absent right seminal vesicle, an atresia of the colon, and a backward projection of the tip of the coccyx (as in the chimpanzee). Huffman, in his case, noted a congenital cystic kidney and also ureters opening ectopically in the bowel. A third case of prepenile scrotum was discovered by Ivar Broman in a photograph of an infant exhibiting a perineal hypospadias. Our own case is the fourth known instance of prepenile scrotum in the literature, and occurred in a double monster with multiple anomalies.

Baby W. was born January 14, 1951 at another hospital and transferred to the Coney Island Hospital January 19, 1951 for study and disposition. Examination on admission disclosed a double parasitic monster (Payopagus Parasiticum) (fig. 1, *A*). This was the first child and first pregnancy of an apparently normal 24 year old mother who conceived 3 months post-maritally following a condom "slip." There had therefore been no problem of sterility. The mother and her parents were free of noticeable anomalies. The past history was negative. The Wassermann and Rh blood factors were not abnormal. The pregnancy was uneventful and delivery occurred spontaneously at term and without mishap. As far as could be determined there had been no exposure to radiation or viral influences. The father was 28 years of age and physically sound, with normal genitalia except for a definite female-type pubic hair arrangement. He denied venereal disease with the exception of a "soft chancre." He had osteomyelitis as a child. There was no knowledge of exposure to radiational or viral agents. Examination of a single wet smear of the prostatic secretions was normal. A single spermiogram revealed: Volume 3 cc; appearance normal; viscosity unusually thin; sperm count 125 million/cc and a total count of 375 million; motility 80 per cent motile in 1 hour; viability (live-dead stain) within normal limits; morphology 85 per cent normal forms; teratological forms of the usual types.

During his stay in the hospital the infant fared poorly, so that it was possible to do only a plain cystogram and a cysto-urethrogram (fig. 1, *B*). Meningeal

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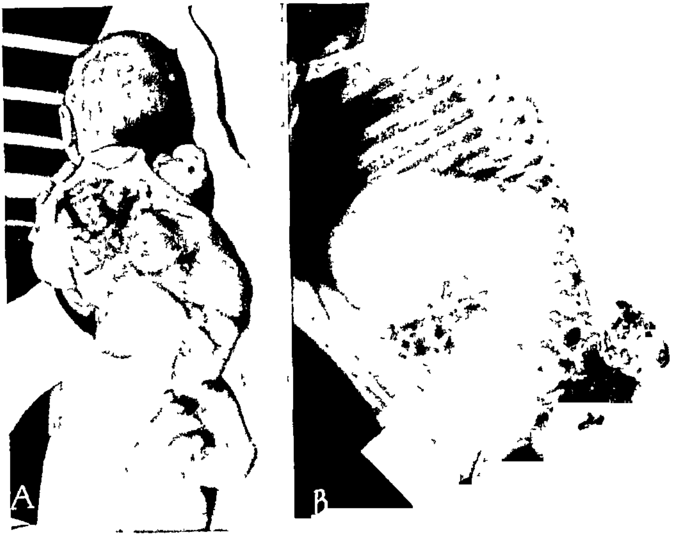

Note incompletely developed parasite consisting trunk attached to lower spine. Note prepenile urethral course visualized by indwelling ureteral catheter between lead shielded scrotum and sacrum. Dye in bladder

symptoms with temperature developed 6 weeks after admission and the child died a week later, having survived 2 months.

Autopsy performed by Dr. Harold Fink revealed a parasitic fetus; hydrocephalus, atrophy left leg and thigh; right talipes equino varus, and the following urogenital findings: There was a well formed scrotum with small firm nodules in each scrotal sac. A postscrotal penis was present with a pinpoint opening at its tip. The skin of the midline genital region was excoriated and there were 3–4 small blind skin sinuses. An anal opening was present. The scrotum contained normal appearing testicles (microscopic not done). The vasa deferentia were present and pursued a normal course to the seminal vesicles. The prostate was average. The urethra was patent and normal. The penis was located posterior to the scrotum. The right kidney showed fetal lobulation. The right ureter was tortuous but patent. There was a congenital absence of the left kidney, ureter, and adrenal. The bladder was normal.

DISCUSSION

Embryologic dynamics. At 4 months intra-uterine life, the scrotal swellings, during the process of fusing to form the definitive scrotal sac, concomitantly shift caudad to assume a position posterior to the formed penis. In the case of prepenile scrotum, however, this shift fails to occur, with the result that the fully developed scrotum assumes a position anterior to the penis.

Prepenile scrotum represents an instance of hysterotely and the scrotal-penis arrangement a hysterotelic feature in development. If such a feature is considered to be one present in the phylogenetic ancestors it is usually described as an atavism or a reversion to type. Goldschmidt explains the dynamics as a shift in the velocity of differentiation of the hysterotelic organs relative to the velocity of general development. The potential for such developmental dyscrasia refers back to gene mutation in the germ plasm. In our case the mutational hysterotely is identified with the external genitals and the phylogenetic ancestor is the Marsupiala in which species prepenile scrotum is the normal organ relationship.

TERATOLOGICAL CONSIDERATIONS

An intelligent approach to prevention of malformations must be through an accurate knowledge of underlying causes. In recent years the problem has been attacked by the experimental method. The sciences of experimental embryology, cytology, genetics, and cytogenetics have slowly yet surely replaced the cruder speculative thinking in the consideration of causality in teratological forms.

In general, normal development in an organism is dependent upon the proper integration and correlation of two prime factors—the germinal (hereditary; gametogenic) and the environmental (zytogenic). The possible role of a third factor—the developing endocrine system—is as yet not clear but appears to be in some way involved in such defections as gynandromorphism and associated sex aberrations. Presumably, a perfect germ plasm developing in a perfect or favorable environment will result in a perfect organism. Conversely, any degree of impairment of one or both of these two factors will eventuate in a variety of teratological forms, be they monsters, anomalies, or simple variations. Some abnormalities are largely due to a faulty germ plasm and are considered "hereditary" (cleft palate, hypospadias, etc.). Others come about mainly because of purely adverse environmental conditions. The bulk of teratological forms, however, originate from the interaction of a faulty germ plasm (ovum or sperm or both) and an unfavorable environment. In any given case it is almost impossible to determine the contribution of each of these factors since they cannot be clearly demarcated. Thus in the case of a double monster, there occurs an interruption at the stage of infolding and production of the primitive streak (beginning gastrula stage). With resumption of normal conditions a second primitive streak is produced and duplicity results. Yet who can say that this tendency was not already predetermined in a faulty germ plasm?

The environment. In so far as the environment is concerned, one or more of several known factors will lead to a condition of unfavorableness. There are for instance the mechanical deterrents to normal growth, such as amniotic bands, constrictions, or folds. Or there may occur alterations in the physico-chemical milieu of the developing zygote due perhaps to changes in oxygen tension, or alterations in pH, or temperature shifts, or even adverse hormone action. Also recognized as influencing the environment are the nutritional factors arising from inadequate food, vitamin or oxygen deficiencies—in some instances brought about by the action of certain viruses or poisons Most important, however, would appear to be the occurrence of so called developmental arrest at some "critical" stage of gestation—notably at the beginning of the gastrula stage and also at the fifth month of intra-uterine life For example, it has been shown that if a mother is exposed to the virus of Rubella at the fifth month of her pregnancy, the resulting offspring will probably be imperfect It is quite possible that a number of drugs, vitamins, and poisons may in like manner upset the necessarily delicate physio chemical balance of intra-uterine physiology and so be instrumental in creating an undesirable environment

Before discussing the role of the germ plasm in maldevelopment it might be apropos to recall that the genito urinary tract is subject to certain other developmental hazards peculiar to itself These are the very factors which also make this apparatus notoriously liable to multiple anomalies, namely 1) the close anatomic relationship of the separately developing urinary and genital systems, 2) the derivation of the genito urinary tract from two tissue fundaments (entoderm and mesoderm), 3) the final emergence of two types of sex organs with the attendant predisposition to gynandromorphism (see endocrine factor above), 4) the genito urinary tract is the classical illustration of Van Baer's Law—the ontogenetic tends to repeat the phylogenetic history in an organism—thus especially predisposing it to all degrees of marsupial atavism (note prepenile scrotum)

The germ plasm Even before being subjected to the possible hazards of an imperfect environment, the developing organism has apparently already been stigmatized by certain primordial and in many cases irreversible potentials inherent in the germ plasm So it is then, that the germinal factor of necessity assumes an all important role in the causality of anomalous forms Genetics and cytogenetics deal with the study of this factor and its relation to heredity

The germinal factor refers specifically to the male and female gametes or sex cells and to the complicated division-reduction process called meiosis (haploid division of the chromosomes) by which they are produced In the male meiosis takes place within the semeniferous tubules during the transformation of the primary spermatocyte (a somatic cell with a full chromosome compliment) into the spermatid (a sex cell with one half the number of chromosomes) The purpose of meiosis, besides the numerical reduction of the chromosomes, is the attraction, the pairing, the interchange, and the separation of the homologous paternal and maternal chromosomes The number, form, and arrangement of the chromosomes of a given species are remarkably constant (in man 48) Within the chromosomes reside the genes These are the highly differentiated ultramicroscopic units of nuclear chromatin material which are directly concerned with variation, heredity, mutation, evolution and in addition they control morphogenesis and body equilibrium Through experimental embryology and cytogenetics it has been established that the gene composition of a given chromosome presents a geographically constant and orderly pattern This pattern constitutes the ' genetic or chromosome map " Study of such maps (in the mouse, hen, corn, and banana fly) has further demonstrated that every physical characteristic has its origin in a gene and that each gene is always in a topographically constant position in the chromosome as well as in unvarying relation to its fellow gene. In the human species it has been possible to localize a series of genes only in the sex chromosomes.

During a normal meiotic progression there occurs (through the mechanism of linkages, chiasmata, and crossing-over) an exchange of hereditary materials with resultant recombination of the homologous genes. This results in a new individual which "resembles" its progenitors. Should normal conditions within the chromosome be upset, there will originate some form of maldevelopment (structural hybrids). More accurately, such departures from the normal are caused by gene mutation with an alteration in the size, form, and shape of the gene. Heredity, in other words, may express itself in normal development based upon a recombination of genes or in an abnormal development originating in a gene mutation.

Gene mutations may be spontaneous in nature or may be induced through radiation. Whatever the stimulus, such alterations in the gene are in most cases undesirable and are especially prone to occur during a "critical" period in the meiotic process. De Robertis cites this specifically within certain stages of interphase and prophase. Most often mutations occur in the recessive genes and far less often is the dominant gene affected, in which case mutant forms always appear in the first generation. In any case the gene is the target of the injurious agent. Moreover, it would appear that during the disruption of a particular chromosome, in addition to changes in the "target" gene, there is brought about an over-all imbalance in the entire genetic map relationship with a likely "spilling-over" of a recessive or hitherto dormant gene. Should the latter represent the primordium of a structure low in the phylogenetic scale (it must be remembered that not all genes possessed by man are human genes) there will emerge an organ-type which is unmistakably atavistic. Such is most likely the explanation for the re-emergence of the marsupial prepenile scrotum.

Spontaneous alterations in the gene composition apparently occur far less often than those induced by radiation. Obstetric records at the Bellevue Hospital, New York City, covering a four year period disclose 118 anatomically abnormal children in 7,865 births. In none of these cases had the mothers received radiation in any form. We must conclude therefore, that this number indicates malformations do arise from environmental causes of which some few may have been determined by spontaneous gene mutation.

On the other hand, mutations can be produced almost at will through neutron radiation of the gonads, either directly or indirectly. Radiation-induced mutations are indistinguishable from those occurring in nature. Muller first directed attention to the undesirable effects of radiation on genetics and produced mutant forms at will in Drosophila by this means. Whether or not we are justified in extrapolating data obtained with lower species is a moot question and geneticists are divided in opinion. Haldane for one believes not. Certainly, because of the nature of man, it has been impossible to demonstrate mutant forms comparable to those produced in the experimentally controlled, and short-lived lesser species

The gonads are affected by neutron radiation in two ways First there is the immediate effect on the testicular cells, and depending upon the dosage with its concomitant chromosomal ionization there will be observed all degrees of histolysis This immediate reaction is both a temporary one and is in all likelihood also reversible Second, and probably most important, there is the delayed or long-term effect upon the nuclear material of the sex cell—gene mutation Our observations to date must rely on the study of cell morphology since we are unable to follow the complicated chain of electrochemical events attendant upon neutron injury We do know that neutron particles possess penetrating properties, that these particles collide with the nitrogen and hydrogen atoms in living tissue to strike off a proton which, as a secondary particle, ionizes the tissue Just what the prime force is and how it acts in bringing about gene mutation we cannot say

In general, the gonads are liable to three types of radiation hazard 1) diagnostic radiation, which is presumably 9/10 ineffective because of absorption in the superficial tissues, 2) therapeutic radiation, in which high voltage ray penetrating doses with low milliamperege and proper filtration are administered, 3) accidental radiation, which includes all degrees of neutron injury ranging from the low dosage normally absorbed in any surrounding atmosphere with its cosmic radiation to give a cumulative effect up to the massive neutron injury inflicted by an atomic explosion

The immediate destructive effects of radiation upon the testicle have been studied from several sources chiefly through examinations by testis biopsy Maximum effects causing extensive destruction of the entire testis have, for example, been noted in men trapped within a 1500 meter perimeter of the conventional (Hiroshima-type) atom bomb explosion Likewise Robinson and Engle reported a case subjected to accidental radiation while engaged in atomic research They noted that all seminiferous elements had been destroyed with the exception of Sertoli cells and some few spermatogonia Charny also, in an effort to stimulate spermatogenesis in deficient males, employed a 28r dose to the testes at weekly intervals for three exposures and described the damaging effects of even such small doses Follow-up in the above instances indicate that there is a tendency to histologic recovery and regeneration and that the physiologic process at that dosage is a reversible one That the immediate histologic effect of radiation is not permanent is also borne out by those cases previously radiated for testis tumor in which reappearance of spermatozoa is subsequently demonstrated The dosage required to produce demonstrable physical damage is of no particular moment since radiation effects on genetics are produced by cumulative dosage without regard to dosage rate or wave length, and in addition, distinctions between microscopic and ultramicroscopic tissue reaction are not feasible In case of direct gonadal radiation Charny suggests that one half of 28r might conceivably not "damage" the testis

From the practical standpoint a consideration of neutron injury to the germ plasm and specifically the gene is of far greater importance. Unfortunately, satisfactory appraisal of the ultimate or long-term results of radiation on genetics is impossible, unless we are prepared to translate to humans such delayed effects as have been observed in work with lower species. In the absence of direct evidence in the human, are we justified in predicting mutant forms in progeny several generations removed? Indeed, there are very few instances of even second generation offspring of radiated mothers. In spite of the fact that the recessive "target" gene would appear to have a progressively decreasing chance of emerging with each succeeding generation, there is no reason to surmise that mutant forms may not appear in considerable numbers in later generations. In support of such a view is the fact that sex-linked mutations are the exception to the general rule that recessives require generations for expression.

O. J. Pollack states that as far as the germ plasm is concerned, "any type of radiationenergy is effective. Theoretically, there is no lower limit. The tolerance dose is a dose which causes 'minimal' mutation (probably —0.25r)." This would indicate that genes are extremely reactive to the least radiational stimulus. Therefore we cannot rest assured that even small radiation dosage will not cause mutations in the ovaries and testes of future generations. In actual practice such small doses are often inadvertently administered to the gonads, especially in the course of extragenital radiation whether it be for diagnostic or therapeutic purposes.

In most cases dosage absorbed by the unprotected gonad may be computed. For example, if one radiates a carcinoma of the lung with x-ray and if the total dose is 12,000r, the ovary in a distance of 21 to 26 cms. will receive 12r —a figure well above the "minimal" mutation dose. The testis, at nearly the same distance but more superficially located will probably absorb an even larger dose. Comparable figures can be produced in the case of such diagnostic procedures as hysterosalpingography, excretory urography, etc. If the gonads receive direct radiation "stimulation" as in the treatment for certain types of amenorrhea, the menstrual cycle is often re-established and even though there are no demonstrable anatomic changes in the ovaries, the dosage employed should be sufficient to effect the germ plasm—since it is adequate to affect a most complex physiological function as menstruation. Yet a comparable dose (one third) is applied to an individual who received an excretory urogram, a retrograde pyelogram and a barium enema. We cannot escape the conviction that even such presumably innocuous procedures are bound to cause gene mutation. In addition, it must be recalled that mutations are not limited to the reproductive cells, but may occur in somatic tissue (biologic mutation). Here mutant areas are made of a size corresponding to the number of descendant cells produced. Evidence that the physiological state of the cell (as, perhaps following radiation) affects the mutation rate is still inadequate, but it is possible that this may turn out to be of very great importance. There is also the question of the possible deleterious effects on gonadal physiology following radiation of the other endocrine glands. The mechanism here is very obscure, yet such a possibility must be kept in mind.

Significance of an abnormal spermiogram A spermiogram was done in our case for the purpose of ascertaining the percentage of morphologically abnormal spermatozoa though an abnormal semen was not anticipated Since one specimen is sufficient to establish the spermiogram pattern in any given individual, it was concluded that this parent produces semen well within the bounds of "normalcy"

As to the genetic significance of an abnormal semen, our present knowledge does not permit of a satisfactory statement However, data are available in support of the conclusion that neither subnormal spermatogenesis nor reproductive disturbances in the female necessarily indicate genetic inferiority Indeed unsatisfactory progeny are not more common among successfully treated sterile couples than among those reproducing without special assistance Disturbances in gametogenesis appear to be caused by deficiencies in the functions required for the production of gametes, and not by deficiencies in the germ plasm Briefly then, genetic inferiority is not necessarily reflected in the sterile or subfecund state In addition, the tendency to early miscarriage in women impregnated by subfecund semen does not involve an increased chance of abnormal progeny, as is noted in those cases in which miscarriage is controlled and pregnancy proceeds to delivery of a normal child

Thus the demonstration of a semen study with a high incidence of abnormal spermatozoa (over 18 per cent) does not indicate an increased chance for maldevelopment The question of what constitutes a "normal" spermatozoon from the genetic point of view cannot be based upon evidence of morphology, motility, and viability alone There is not reason to believe that an "abnormal" spermatozoon may not successfully fertilize an ovum with the consequent production of normal offspring, given of course a normal germ plasm and a favorable environment

SUMMARY

Since mutations are predominantly undesirable and their expression deleterious to the race, and since radiation induced mutations are far in excess of those spontaneously produced, every effort directed to the minimizing, if not the elimination, of radiation hazards will be a long step towards the prevention of maldevelopment In the words of Muller, "like most species, we are already encumbered by countless undesirable mutations, from which no individual is immune" In this situation we should draw the practical lesson that because the great majority of mutations are undesirable, their further random production in ourselves should so far as possible be rigorously avoided Radiologists and their technicians receive a dosage of about 16 to 30r per day despite present available protective measures It becomes an obligation for radiologists to insist that the utmost in precautions be taken which are necessary for shielding the gonads, be it in industry or in medical practice

CONCLUSION

A case of prepenile scrotum in a double monster is presented Embryologic and teratologic aspects were discussed Short term and possible lasting effects of varying doses of radiation on the gonads were considered; in particular as regards neutron injury to the germ plasm. The questionable significance of an abnormal spermiogram was reviewed. A plea is made for the judicious use of any form of radiation in medical practice. In the case of urologists, x-ray examinations may profitably be limited to the bare essentials and the present practice of repeat examinations be kept to a minimum.

3420 Avenue J, Brooklyn 10, N. Y.

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CLINICAL APPLICATION OF BLOOD VOLUME STUDIES IN MAJOR SURGERY

CHARLES M BARBOUR, JR AND ROBERT TENNANT

Departments of Anesthesiology and Pathology, Hartford Hospital, Hartford, Conn

Studies of blood volume provide information of greater usefulness in the valuation and management of surgical patients than other hematologic procedures currently employed Four years experience with the Evans' Blue (T-1824) Dye Method emphasizes the important role it plays in evaluation and preparation of patients for performance of operative procedures Recognition and correction of quantitative and qualitative deficits or excesses of blood volume have resulted in marked improvement of optimal physiologic conditions during operation Anesthesiologists are granted wider range of selectivity of agents and techniques, surgeons are offered greater peace of mind, and patients are guaranteed the benefits of greater safety Provided replacement therapy is guided by this procedure, smoothness and rapidity of convalescence can be assured with greater certainty

The six common abnormalities of blood volume encountered among urologic patients as illustrated, are acute hemorrhage, compensated anemia, syndrome of chronic shock, hemoconcentration, hydremia and absolute polycythemia For purposes of clarity consider the seven schematic representations to be hematocrit tubes into which one's volume of circulating blood has been placed (fig 1) The blackened areas below represent the volume of red cells The cross hatched portions above represent the volume of plasma The lower two interrupted horizontal lines are the limits of normal red cell volume Normal range of plasma volume falls within the upper two interrupted horizontal lines

In the center is the schematic representation of the blood volume of the normal patient To the left are three common causes of deficits in blood volume, namely, acute hemorrhage, blood loss compensated by hemodilution and the syndrome of chronic shock To the right of the normal are the two common causes of excesses of blood volume—hydremia and absolute polycythemia Hemoconcentration is included with the excesses of blood volume because the elevated hematocrit readily confuses it with absolute polycythemia

Despite the presence of normal values for the hematocrit, deficits of both red cell volume and plasma volume exist following acute hemorrhage, and with the syndrome of chronic shock Patients with compensated anemia have deficits of red cell volume and an excess of plasma Values for the hematocrit are therefore low Again they are not reliable guides for therapy because hemodilution exaggerates the magnitude of the anemia In the presence of dehydration the exact opposite is true Deficits of circulating plasma in the presence of normal volume of red cells produce marked elevations of the hematocrit It is necessary to eliminate the possibility that this indicates the presence of polycythemia Hydremia is characterized by excessive volumes of plasma Because the volume of red cells

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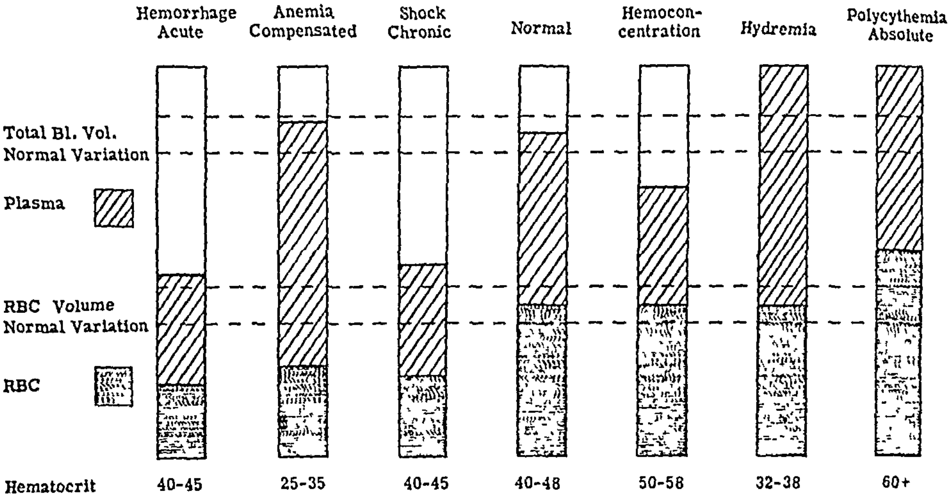

FIG. 1

is within normal limits, values for the hematocrit and other tests of concentration are low. Hydremia therefore simulates the clinical picture of anemia.

Absolute polycythemia, both primary and secondary, is characterized by an excessive volume of red cells. Polycythemia vera is further characterized by normal volume of plasma and elevation of the platelet count. Secondary polycythemia, as found in patients with chronic pulmonary, chronic or congenital heart disease and accompanying some renal and adrenal tumors, may have excessive volumes of both red cells and plasma.

ACUTE HEMORRHAGE

These illustrations emphasize the significant fact that the hematocrit is not *truly indicative of existing deficits or excesses of blood volume*—unless the volume of circulating plasma is within limits of normal. Acute hemorrhage presents an excellent example of this fact.

1) Immediately following acute hemorrhage values for the hematocrit, percentage of hemoglobin and red cell counts remain within normal limits. They are therefore of no value as guides for replacement therapy.

2) Studies of blood volume indicate the quantity of whole blood required to prevent development or continuance of shock. Shock is avoided, or effectively treated, by prompt quantitative administration of whole blood.

3) Thirty per cent reductions of total blood volume in the normal patient are accompanied by onset of shock.

4) For patients with existing deficits of blood volume—loss of smaller amounts of blood produce shock.

5) Studies of blood volume are of great value in the differential diagnosis of shock produced by causes other than loss of blood—such as bacteremia.

6) Immediate treatment of acute loss of blood differs from that required after four to eight hours have elapsed.

Studies of blood volume bring to light glaring errors made in replacement therapy. They make it possible to use blood more efficiently for information is provided regarding qualitative as well as quantitative requirements of patients with anemia Unless deficits of blood volume are recognized and replenished according to specific indications maintenance of optimal physiologic conditions during operation cannot prevail Use of transfusions of packed red cells rather than whole blood for anemic individuals whose volume of plasma is normal is a refinement which improves care of surgical patients

COMPENSATED ANEMIA

Proceeding to the second portion of the illustration, compensated anemia differs from acute hemorrhage in that

1) Within eight to twelve hours following acute hemorrhage, fluid from the interstitial spaces enters the vascular tree to restore total blood volume to normal Compensated anemia is frequently encountered in patients in whom hematopoiesis cannot adequately replace blood loss due to chronic bleeding or destruction of red cells

2) The hematocrit will indicate the presence, but not the magnitude of deficits of red cell volume

3) Studies of blood volume indicate the need for transfusions of packed red cells or red cells suspended in saline or glucose

4) Hypervolemia is avoided by such qualitative therapy Cardiac failure, pulmonary or cerebral edema and renal insufficiency may therefore be avoided

5) Replacement therapy for compensated anemia must be qualitative as well as quantitative

Errors of clinical judgment are avoided by employment of studies of blood volume to supplement knowledge gained by a critical evaluation of the patient's history and physical status Experience emphasizes the significant fact that sizeable deficits of red cell and plasma volume exist when values for the hematocrit, percentage of hemoglobin and red cell count are normal Formerly we blindly considered such hematologic reports to indicate that patients possessed normal amounts of blood We are now aware that many of these patients developed shock during or immediately following operation because they had real deficits of blood volume when they entered the operating room This was particularly true of elderly, debilitated or chronically ill patients who presented what is now described as the syndrome of chronic shock This syndrome presents a treacherous situation for none of the signs and symptoms of shock are exhibited till the characteristic susceptibility to vascular collapse is made manifest by the added stress of anesthetic and operative procedures

CHRONIC SHOCK

The third schematic representation from your left depicts the syndrome of chronic shock 1) It is characterized by loss of weight, reduction of blood volume, increased volume of interstitial fluid and depletion of tissue and plasma protein It is found in patients with chronic infection, malnutrition and malignant disease, especially when metastases are present

2) Susceptibility to development to shock makes these patients poor surgical risks Loss of but small amounts of blood produces hypotension

3) The hematocrit is not indicative of existing deficits of red cell and plasma volume

4) Preoperative replacement of deficits of whole blood avoids shock.

5) Wound healing and convalescence is hastened by the indicated therapy. In the presence of anemia, fabrication of hemoglobin has priority over manufacture of tissue protein. Transfusions are therefore needed to hasten wound healing.

Attention has recently been focused upon the importance of prompt recognition of excesses of blood volume and hemoconcentration. It is becoming increasingly evident that hemoconcentration and hypervolemia produce complications that are potentially more serious than the untoward effects of anemia. Increased viscosity, slowing of circulation, inadequate oxygenation of tissues, formation of thrombi and the hazard of embolic phenomena render patients having dehydration or polycythemia poor surgical risks. Serious complications result unless excesses of red cell volume are detected and corrected prior to operation. Induction of general anesthesia is difficult and maintenance is complicated by the presence of labored respiratory function, cyanosis, hypertension, increased venous pressure and the threat of serious cardiac or cerebrovascular accidents. Marked vascular congestion due to hypervolemia results in excessive bleeding at the site of trauma, and into incised areas. Formation of hematomas in the postoperative period are not uncommon. In our experience hemoconcentration and hypervolemia are common findings. Their presence must be considered potentially hazardous to the well-being of patients.

HEMOCONCENTRATION

1) Immediately to the right of the schematic representation of the normal is the drawing of hemoconcentration. In our series of 460 patients having hematocrits of 50 or above, 25 per cent had dehydration due to loss of circulating plasma.

2) Studies of blood volume differentiate between hemoconcentration due to dehydration and that produced by hypervolemia.

3) Adequate hydration readily corrects hemoconcentration due to loss of plasma and eliminates the harmful effects of increased viscosity.

4) Hemoconcentration due to dehydration or hypervolemia may precipitate the onset of thrombophlebitis, coronary or cerebral thrombosis. This suggests that hemoconcentration plays a significant role in the etiology of these diseases, and implies that we are over-cautious in restriction of fluids for these patients.

HYDREMIA

The sixth portion of the slide depicts findings in hydremia.

1) Physiologic hydremia accounts for apparent anemias of pregnancy.

2) Pathologic hydremia exists in patients with cirrhosis of the liver, renal insufficiency and following excessive fluid therapy.

3) Circulatory overload is the real hazard if therapy is guided by values of the hematocrit. Blood volume studies are indicated as a diagnostic aid and to guide therapy.

POLYCYTHEMIA

The last schematic representation is that of polycythemia.

1) Polycythemia vera is characterized by an increased volume of red cells and elevation of the platelet count.

2) Presence of increased viscosity facilitates intravascular coagulation and favors development of thrombosis and embolic phenomena

3) Hypervolemia leads to profuse hemorrhage due to trauma and during operation

4) These untoward effects of hemoconcentration and hypervolemia are eliminated by performance of repeated phlebotomies

5) Otherwise administration of general anesthesia and performance of elective operative procedures are contra indicated In emergency, or in the presence of uncorrected hypervolemia, regional anesthesia, including spinal, is indicated

6) In the absence of chronic or congenital heart disease repeated, controlled daily phlebotomies can be performed without untoward effects Normal fluid and electrolyte balance, however, must be maintained

7) This regimen results in improvement of the general health of patients by elimination of headaches, sensations of fullness of the head, dizziness, syncope and pain in the extremities

SECONDARY POLYCYTHEMIA

1) Chronic hypoxia due to chronic pulmonary, chronic heart disease as well as the presence of some renal and adrenal tumors theoretically set the stage for development of secondary polycythemia

2) In the presence of chronic or congenital heart disease repeated, controlled phlebotomies (every third day) can be performed Blood volume should be reduced to that optimal level which does not produce weakness, dizziness or syncope

3) Controlled phlebotomies of 250 cc each are recommended to reduce hemo concentration and hypervolemia to that level which permits optimal physiolgic function

4) Following removal of renal or adrenal tumors secondary polycythemia may disappear

ARTIFICIALLY INDUCED POLYCYTHEMIA

1) Circulatory overload due to excessive transfusions are likely to occur in the absence of guides such as determination of blood volume

2) Pulmonary edema, cerebral edema, cardiac failure and cerebrovascular accidents are prone to develop The resulting increased viscosity leads to myocardial inefficiency and shock Removal of the excess blood is indicated to combat shock

SUMMARY

An attempt has been made to present in concentrated fashion, variations in the status of blood volume It has been demonstrated that values for the hemato crit can be misleading Need for determination of blood volume in preparation of patients for operation, and as a factor in the control of intravenous therapy during and after operation has been emphasized Our experience has been that compensated anemia is a frequent finding among urologic patients for whom operative procedures such as transurethral resection have been performed It is hoped that the facts presented will assist urologic surgeons to extend their interest in the total fluid economy of patients

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IMPROVED CYSTOSCOPIC FIELD ILLUMINATION

JULIUS H. WINER

From the Division of Urology, University of California Medical Center, Los Angeles, Calif.

I would like to present a method to increase illumination of the cystoscopic field.

It occurred to me that much light radiation from cystoscopic lamps is wasted by dispersion into areas not included in visual fields and by absorption into the dull finished walls of the cystoscope and resectoscope sheaths.

The illumination of the bladder and urethral fields of vision can be intensified by using a light reflector to make use of otherwise dissipated light.

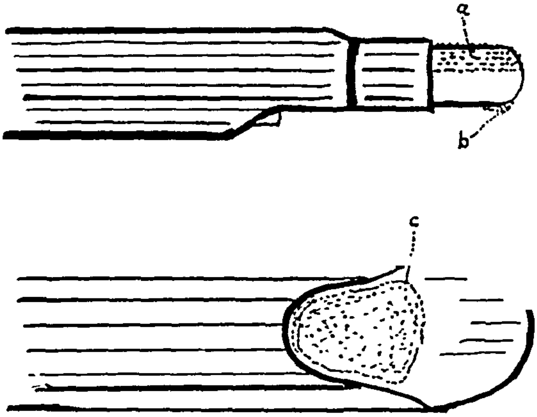

FIG. 1

As a "reflector," pure white lacquer of a highly refractile, nonconductive plastic has been painted on the back of the lamp; i.e. that part of the lamp not directly facing the cystoscopic field (fig. 1, *a*). This has given increased brilliance to the fields visualized in the bladder and urethra. Silver "mirroring" of this portion of the lamp has also been done, but the possibility of current conduction prevents general usage.

A similar "reflector" has been used, applied directly to the brown bakelite resectoscope sheaths (fig. 1, *c*). A shiny aluminum lacquer has also been painted on the portions of metal sheaths adjacent to the lamps.

Use of the same types of reflectors for ordinary room lighting lamps saves up to 70 per cent of the otherwise wasted candle power.

Additional concentration of illumination to spot areas in the visual field has also been obtained by using a clear plastic lacquer to form a convex lens on the front of the cystoscope lamp, focusing a spot light on a smaller portion of the visual field (fig. 1, *b*).

9915 Santa Monica Blvd., Beverly Hills, Calif.

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LOCATION OF LOCOMOTION ENERGY-AREAS IN HUMAN SPERM

ROYAL L BROWN

This study is concerned with locating the area or areas in human sperm which provide the necessary energy for their locomotion a significant function prerequisite to fertilization Sperm are uniquely adaptable to such a study in that spermiogenic alterations, e g , the metamorphosis of an immobile spermatid to a mobile sperm, is fairly well established, and the dynamic development of its locomotor structures may be microscopically observed and pertinent organelles accurately identified with their antecedents[1] [2]

HISTORY AND PROBLEM EVALUATION

A comparison of the duration of locomotion between morphological segments of a cell to indicate energy areas or centers has not previously been attempted with sperm, nor productively in other motile cells Neither has freezing (dry ice) and thawing as a technique for the segmenting of cells been used previously in similar studies

Functionally, the characteristic energy producing metabolism of sperm is maintained primarily by intracellular enzymes, with probably some extracellular enzymatic processes[3] Aerobic respiration in sperm with its increased energy release occurs variably among species and within the same species during quantitative change in activity As evidence, the glycoltyic anaerobic processes in the sperm of man[4] is reported as only five per cent that for bovine[5], yet in Ringer-phosphate glucose solution, aerobic glycolysis by human sperm is eighty to ninety per cent of that accomplished anaerobically[3] Potentially, human sperm appear able to appropriately utilize either method for respiratory energy, but throughout its spermatogenic life relies primarily on anerobic glycolysis Exclusion of air as oxygen source does not significantly alter the longevity of human sperm ejaculated under paraffin oil[6]

The determined enzymes present are cytochrome a, b, and c, succinic dehydrogenase, adenosine phosphates, hyaluronidase,[7] and presumably other enzymes and co enzymes essential to the characteristic anaerobic and aerobic respiratory gylcolysis of sperm[8]

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METHOD AND TECHNIQUE

The sperm were segmented by freezing.[6] A small drop (0.04 cc, measured in a uniform capillary tube)[9] of recent ejaculate[10] was placed on each of thirty-three slides or slips, frozen with liquid nitrogen or carbon dioxide and thawed out at room temperature as needed after varying time intervals (1–200 hours.)[11] Comparable controls were prepared without freezing and the spermicidal times determined.[12] A third of the slides or slips were subjected to each of three spermicidal procedures: 1) one part semen to one part 2.8 per cent (0.14 molar) aquous potassium acid phthalate as buffered spermicide, pH 4.0[13] and maintained at room temperature (26–29°C) during the determination of spermicidal times[14]; 2) semen alone maintained at 37°C temperature as spermicide[15]; and 3) semen alone maintained at room temperature.[16] The spermicidal times of each series of three slides, as indicated above, were determined independently by periodically observing each preparation microscopically for the presence or absence of sperm locomotion.[17] Cessation of motion of the tail or its segments served as the end point.[18] The time interval required to thus immobilize sperm or tail segments was considered to be equivalent to the spermicidal time or longevity,[19] and served to localize the site of origin of locomotion energy.

The comparison of the spermicidal times of a control with a test series was done in order to detect any spermicidal or devitalizing effect from freezing and thawing alone. The test sperm, by these applied procedures, were largely killed outright (85 ±10 per cent), probably due to lethal, structural or metabolic disarrangements; others were devitalized as indicated by their decreased spermicidal times; some few remained detectably unaffected. Many sperm which remained alive were segmented, both segments surviving. These segments resulted from complete fractures at select, vulnerable sites. In order of frequency, fractures occurred at: 1) the head and middle-piece junction, 2) middle-piece and tail junction, and 3) transversely without select sites throughout the length of the tail. Living segments which contained a piece or all of the tail characteristically maintained normal locomotion. This served in this experiment as the evident and measured energy-utilizing function.

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Because of the relatively few sperm and segments remaining mobile after freezing and thawing, the autogamous segments i.e., segments from the same sperm, could be identified in some instances, and their spermicidal time or longevity directly compared. Furthermore, on slides in which no chemical spermicide (potassium acid phthalate) was added, and thus no mixing after thawing, these

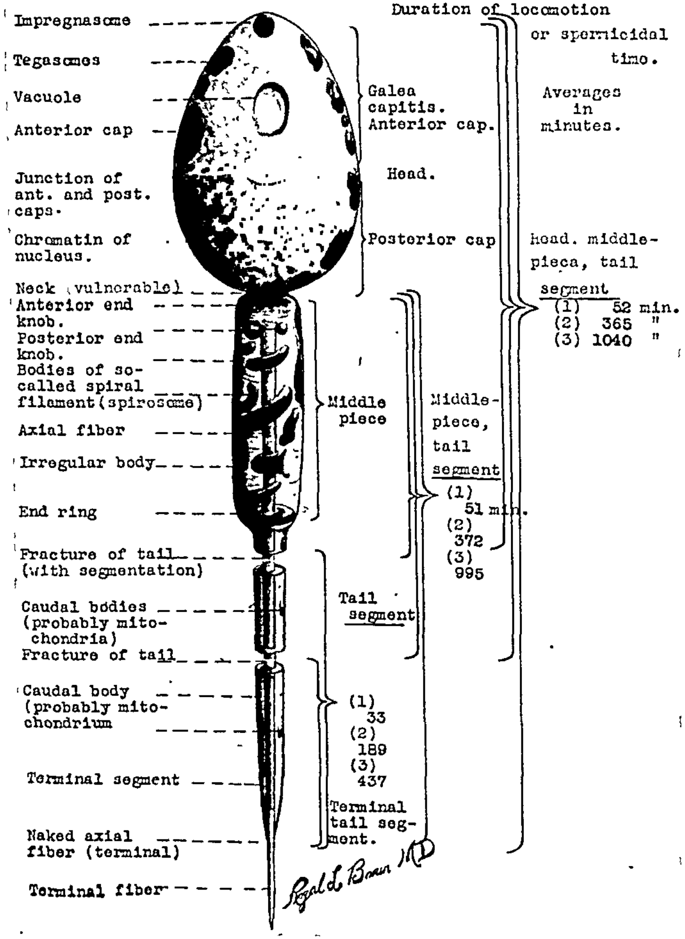
Impregnasome
Tegasomes
Vacuole
Anterior cap
Junction of ant. and post. caps.
Chromatin of nucleus.
Neck (vulnerable)
Anterior end knob.
Posterior end knob.
Bodies of so-called spiral filament (spirosome)
Axial fiber
Irregular body
End ring
Fracture of tail (with segmentation)
Caudal bodies (probably mitochondria)
Fracture of tail
Caudal body (probably mitochondrium
Terminal segment
Naked axial fiber (terminal)
Terminal fiber
Galea capitis. Anterior cap.
Head.
Posterior cap
Middle piece
Tail segment
(1) 33 (2) 189 (3) 437
Terminal tail segment.
Middle-piece, tail segment
(1) 51 min. (2) 372 (3) 995
Duration of locomotion or spermicidal time.
Averages in minutes.
head. middle-piece, tail segment
(1) 52 min.
(2) 365 "
(3) 1040 "
Royal L. Brown MD

FIG. 1

autogamous segments conveniently remained in the near vicinity of each other on the slide. Thus comparison of the accurately determined time interval of sustained locomotion by these sperm segments suggested structural centers of origin for the energy involved in their locomotion.

Direct comparisons of duration of locomotion in segments of a single sperm were accomplished in but five instances, as these segments necessarily had to remain within a locatable microscopic area, and be identifiable. Nevertheless, the uniform sequential immobilization of sperm segments, autogamous or not, indicates directly a difference in sustained locomotion of these segments, and thereby delineates areas which in all probability function in providing energy for locomotion (fig. 1). Several hundred living sperm observed on thirty-three slides gave consistent results.

RESULTS

Sperm which survived thawing had a five to fifty per cent reduced spermicidal time when compared with the control sperm of the same ejaculate. The conditions which appeared most influential in reducing spermicidal time were their retention in the frozen state and protracted spermicidal testing, e.g., tests done at room temperature. Parenthetically, lengevity or the post ejaculate period of survival was markedly increased in the sperm stored in the frozen state: their survival time was two weeks (maximum storage) plus their spermicidal time or 21,160 minutes as compared with 1,564 minutes for the control spermicidal time. Decreased rate of metabolism of intrinsically limited substrates probably accounted for this prolonged longevity of frozen sperm.

Thawed sperm, whether morphologically intact or brachycaudate (shortened tail), had comparable longevity (average 52, 365, and 1,040 minutes) as determined by sustained locomotion using the three spermicidal procedures. Tail segments with the middle-piece attached had similar spermicidal times (average 51, 372, and 995 minutes). Segments caudad to the middle-piece had decreased times (average 33, 189, and 437 minutes) irrespective of the tail area involved (fig. 1).

The five autogamous segments containing the middle-piece survived 395, 338, 342, 354, and 366 minutes as compared with 192, 166, 165, 172, and 176 minutes respectively for the tail segments. The average time is 357 and 174 minutes respectively; or, using the tail time as unity, a ratio of 1:2 for the five autogamous segments and 1:1.95 for all segments. Summarily, the presence or absence of the nucleus (head) did not alter the duration of locomotion of mature sperm: the presence or absence of the middle-piece did.

DISCUSSION

Fracturing. Slow freezing as well as slow thawing of the sperm crystallized intracellular water, thereby tearing and cutting cell structures by the expansion of forming ice crystals. Cell segmentation resulted. Intra- and extracellular expansion co-efficient differences could account for preponderant characteristic fracturing at the neck site with decapitation. Interestingly, no living cell was observed which sustained a ruptured head or middle-piece; the delimiting membranes, thickened by cap formation in spermiogenesis,[20] invariably remained intact except at critical junctions In a few instances an incomplete fracture of the tail resulted in a continuity resembling a "green stick" fracture

Fracture regions Neck fractures were common and complete The entire middle piece with "spirosomes", axial fiber, anterior, posterior, and ring centrosomes remained intact and within the delimiting membrane in all studied specimens (fig 1) The caudad axial fiber, composed of several filaments,[21] was not noted to be fractured alone but appeared invariably to involve peripheral structures Not always, however, did the transverse tail fracture necessarily include all successive structures, at a single locus as evidence, in one observed instance the axial fiber of a brachycaudate segment extended beyond the fractured tail sheath for approximately three micra

In the few observed "green-stick" fractures the locomotion of the two incompletely separated segments, insofar as could be determined, was continuously synchronous, as if uninterrupted The effect of discontinuity of the axial fiber without peripheral structure involvement on synchronicity of flagellation during locomotion was not observed that fractures of the fiber do not detectably alter characteristic flagellation of the resulting independent segments, however, is definite Energy substrate for flagellation including initiatory mechanism therefore must be independently present in these segments

Locomotion and motion The typical flagellating motion of intact sperm persisted after thawing in locomoting forms Motion at the head middle piece junction in brachycaudate forms (approximately 3 μ) was slow and "jerky", but directional contrastingly, the motion or excursions of the middle piece in intact flagellating forms is more limited In specimens wherein a small area of the tail had been desheathed the bare axial fiber flagellated synchronously with the ensheathed tail The axial fiber, therefore, is dynamically concerned in flagellation In actively flagellating decapitate forms the middle-piece, which is now terminal, was passively waved with the undulations of the tail in contrast, the tail only ordinarily actively undulated in intact forms

Flow of semen under the slip of activators, e g , diluted acids, distilled water, histamine, and several quinones, increased the rate and excursion of flagellation of intact sperm and segments alike Orientation to a counter current position with the anterior end directed "upstream" was present in all forms having heads, to a much lesser degree with decapitate segments and even less or not at all in tail segments

Exclusion of possible energy sites The nucleus is of no immediate significance in sperm locomotion if intrinsically significant, its specific contribution is in some previous and undetermined manner In evidence, decapitated, in comparison to intact forms, are equally dynamic, possess comparable locomotion longevity, may manifest recovery as do some sperm previously immobilized by acid spermicides, and demonstrate identical locomotion insofar as visably detectible.

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Independent locomotion of sperm segments may suggest the axial fiber as a possible site in that it is structurally present in both middle-piece and tail. Its progenitors, the centrioles, are frequently dynamic as evidenced in: 1) their migration to the mitotic poles of dividing cells, or, 2) to the middle-piece in spermiogenesis, 3) their participation in chromosome movement during mitosis and meiosis, and 4) their entering into sperm locomotion through the derived axial fiber. That the axial fiber does not supply its own energy, however, is quantitatively evidenced by the disparity of length of structure and duration of locomotion between the tail and the middle-piece, i.e., the tail with a much longer segment of axial fiber than the middle-piece (approximately 3:1) has a shorter duration of locomotion and spermicidal time (approximately 1:2). Added substrate, e.g., glucose, does not alter this nonreciprocal relationship. If the energy site were centred quantitatively in the axial fiber, the spermicidal time, the longevity, and the locomotion duration probably would not conform to figures obtained for the represented segments (fig. 1).

This evidence, however, does not exclude the axial fiber with its lipid containing fibrillar structure[2] as materially instrumental in flagellating the tail in locomotion. In fact, electrical potentials established by an extrinsic source of energy comparable to the energy source of the myofibrils[22] may remain a plausible explanation.

The submicroscopic particles of the cytoplasm with their known enzymatic activity (esterification[23]) inadequately explains the disparity of this structure-function relationship, and can hardly be credited as an energy site for locomotion. Further, during spermiogenesis, the sperm cytoplast with its submicroscopic particles is largely sloughed off posteriorly and exists extracellularly as seminal detritus.[2] That these extracellular constituents do not serve as the site of locomotion energy is evident from the difference in duration of locomotion between segments with and without middle-piece. Furthermore, sperm presumably washed free of submicroscopic particulate containing detritus and suspended in an appropriate synthetic medium locomote normally without unduly altered longevity and spermicidal time.

Similarly, neither cell membrane potentials nor centrioles *per se* adequately explain the empirical results.

Location of energy sites. Mitochondria are present in both the middle-piece and the tail[2, 20] as identifiable units and preponderantly in the middle-piece as the modified spirosomes* ("spiral filaments"). Their distribution more nearly conforms to the determined data than can any other contained organelle.

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* Because of the erroneous connotation of both "spiral" and "filament", it is suggested that the term spirosomes be substituted: in justification, 1) it considers precedent, however erroneous, 2) it implies their unitary, "somal" nature, 3) their respiratory function, and 4) conforms with other applied nomenclature, e.g., tegosome, centrosome, acrosome, and impregnasome.

Mitochondria contain enzymes and substrate essential to the postulated function.[24] These are cytochrome a, b, and c, succinic dehydrogenase, peroxidase, and cytochrome oxidase, as well as succinoxidase, ATP, ADP, and AMP, riboflavin, α glycerophosphate dehydrogenase, d-amino acid oxidase, ribonuclease and the enzyme complex which oxidizes fatty acid.[25] These constitute essential respiratory enzymes which together with available substrate produce energy. Transfer of this energy through the energy rich phosphate intermediates of glycolysis appears to be the principal and essential manner in which locomotion is energized. The comparative quantitative distribution of mitochondria and substrate in the middle piece and the tail offers an explanation for the difference in spermicidal times and longevity between sperm segments with an without a middle-piece.

SUMMARY

This study ascribes to the middle piece the function of providing the major part of locomotion energy.

The tail (flagellum) also intrinsically possesses energy producing potentialities for locomotion, but to a lesser degree.

The derived evidence confirms for sperm the scanty previous biochemical observations which characterize mitochondria in general as significant enzymatic (respiratory) centers and ascribes to them exothermic reactions.

The energy made available through these energy-rich phosphate bonds appears to be translated into mechanical locomotion through the instrumentality of the axial fiber.

3956 Oakwood Place, Riverside, Calif.

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A TRACTION FOLEY CATHETER

NATHAN CHASET

In the many approaches to the surgery of the prostate gland, the common denominator of all is the control of bleeding following operation. Many methods and many devices have been proposed for this purpose, and a completely satisfactory method has not yet been found.

Since 1950 I have been using a traction catheter which is merely the usual 24F Foley catheter with a traction loop attached to the body of the catheter so that traction may be applied to the catheter without in any way interfering with the drainage through it (fig. 1). The loop is attached to the catheter 18 cm. from the urethral side of the balloon. This provides adequate length so that after tension is released, the loop still stays clear of the urethral meatus.

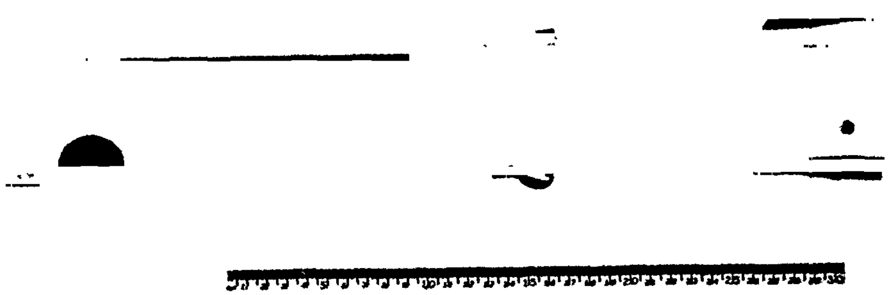

FIG. 1

In the usual suprapubic prostatectomy, I use this catheter in conjunction with a seven inch Oxycel Foley Cone around the balloon and then attach the traction loop to a Prather basket with silk thread. Thus an effective method is provided for the control of hemorrhage from the prostatic bed, and also allows for irrigation through the catheter while maintaining traction. I have used this catheter also in cases in which there was primary closure of the bladder with no suprapubic drainage, and have found it very satisfactory.

This catheter could be used in any case where the combination of traction plus drainage was desirable. It would seem to be ideal for use in rupture of the urethra with displacement of the prostate, but I have not yet encountered such a case.

This catheter is manufactured by the Davol Rubber Co. and is obtainable through C. R. Bard, Inc.

I wish to thank Mr. Leon Nodine of the Davol Rubber Co. for his most kind co-operation in the development of this catheter.

105 Keene St., Providence 6, R. I.

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GROUND SUBSTANCE AND CALCIFICATION THE INFLUENCE OF DYE BINDING ON EXPERIMENTAL NEPHROCALCINOSIS

ROGER BAKER * GERALD REAVEN AND JOHN SAWYER

From the Department of Surgery (Division of Urology) the University of Chicago, Chicago 37, Ill

Clinically, renal calcification is associated with various conditions Renal calculi are not infrequently observed in the presence of obstructive uropathy, prolonged bed rest, and persistent or recurrent pyelonephritis due to gram negative bacteria thriving in an alkaline urine Renal tuberculosis is often associated with secondary calcification Gout frequently produces nephrocalcinosis or uric acid stones Hyperparathyroidism causes nephrocalcinosis or renal calculi in about thirty per cent of patients Evidence is now sufficiently convincing to conclude that prolonged dehydration predisposes toward the formation of calculi In many patients, however, the factor responsible for the development of renal calcification is obscure Although a wide variety of conditions may produce pathological calcification, yet the basic mechanism involved remains unknown Once the etiologic factor has been initiated, it is possible that one biochemical process is common to all types of renal calcification namely, an alteration in the connective tissue ground substance This paper presents data concerning experimental nephrocalcinosis produced by administration of parathormone and demonstrates its selective action on the ground substance The increased susceptibility to calcification of connective tissue ground substance that is depolymerized or altered by toluidine blue is also investigated

Rubin and Howard observed that there is a relationship between the state of connective tissue and the ability of the tissue to become calcified They contend that more reactive groups are available to bind with calcium when the matrix is being depolymerized The basic dye toluidine blue is known to combine with mucopolysaccharides of the ground substance Sylven and others believe this is due to the presence of chondroitin sulfate In bone, toluidine blue binds on reactive groups of the ground substance coinciding with calcified portions of the matrix Furthermore, in three week old rats in which calcification has not yet appeared, toluidine blue binds intensely with the matrix in precisely the geographical locations eventually to become calcified Miller, et al have shown that in vitro calcification of rachitic rat cartilage is blocked by toluidine blue These authors have demonstrated that this inhibition of calcification is directly proportional to the amount of toluidine blue present in the system Marc and Wenck and France have reported that crystallization of certain inorganic salts from a supersaturated solution are markedly inhibited by dyes which stain the mother crystal

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Read by invitation at annual meeting American Urological Association, St Louis, Mo May 14 1953

* Present address Surgical Research Laboratory, Georgetown Medical School Washington D C

METHODS

Young rats of the Sprague-Dawley strain, weighing 200–250 gm. and of the same sex were used in the experiment. They were maintained on a routine laboratory diet and given water ad libitum. The animals were given parathyroid extract (Lilly) as described by Chown, in divided doses over a two-week period. Four groups of animals were studied.

Group I. (Quantitation of the parathyroid effect.) Ten rats received a total of 1,000 units of parathormone; ten rats received a total of 1,300 units of parathormone; twelve rats received a total of 1,625 units of parathormone.

Group II. (Effect on nephrocalcinosis produced by altering ground substance.)

A. Fifteen rats received a total of 1,000 units of parathormone and also 3 cc (intraperitoneally) of a 0.04 per cent solution of toluidine blue, each injection day, for 2 weeks. Fifteen other rats received the same amounts of toluidine blue, but a total of 1,625 units of parathormone.

B. Five rats received 1.5 mg. of desoxycorticosterone acetate each day for a two-week period in addition to a total dosage of 1,625 units of parathormone.

C. Using ether anesthesia, unilateral nephrectomy was performed on ten rats and following this a total of 1,000 units of parathormone were administered over a two-week period.

Group III. (The effect of increased serum calcium levels on renal calcification.)

A. One gram of dibasic calcium phosphate was implanted intramuscularly in 10 rats and was allowed to remain for a 2-week period, at the end of which time the animals were sacrificed. Serum calcium and total protein concentrations were obtained on these animals.

B. A series of 10 rats were injected intraperitoneally with 1.5 cc of a 10 per cent calcium gluconate solution over a 2-week period. A total of 206 mg. of calcium gluconate was injected (13.5 mg. of calcium ion) into each rat. Another series of 10 rats were given the same daily injection of calcium gluconate, but were followed for 4 weeks. A total of 1,775 mg. of calcium gluconate was administered to these animals (90 mg. of calcium ion). Serum calcium and total protein determinations were obtained.

Group IV. (Control series.) Control animals for each experiment consisted of 5 animals that received no injection, 5 rats that received 0.9 per cent sodium chloride intraperitoneally, and 5 animals that received only parathormone in the identical dosage as used in the experimental rats.

At the end of the 2-week period for each experiment the animals were sacrificed by a blow on the head. Blocks of tissue from the kidneys, spleen, stomach, blood vessels and heart were immersed in 95 per cent alcohol and stained by the Von Kossa method. This technique stains inorganic phosphates and carbonates black. These ions are apparently present in the form of their calcium salts. Routine hematoxylin and eosin stains were also obtained.

In order to quantitate the amount of calcium deposited in the kidney, four degrees of scoring were chosen. Those sections classified as 0 represent the stage at which no calcification, or at the most only small flecks of calcium, was seen in a few peritubular basement membranes One plus refers to appreciable calcification, that was still localized peritubularly When the calcium deposition appeared in the basement membrane and also in the lumen of the tubules, it was termed 2 plus, and 3 plus refers to the situation in which the calcification was so extensive throughout the kidney that it was impossible to determine its exact location

RESULTS

I *Quantitation of the parathyroid effect* The production of metastatic calcification by the administration of parathyroid extract is dependent upon both the amount of parathormone given and the duration of the experiment Eight hundred units of parathormone would not produce calcification in one week If the 800 units had been preceded by 400 units the week before, however, calcification would occur This was not necessarily attributed to a greater hypercalcemia, as the serum calcium level returned to normal during the 2 day interval between the two injection periods It seems reasonable that the 400 units of parathormone in some way prepared the tissue for the deposition of calcium The following data obtain using an experimental period of 2 weeks

One thousand units of parathormone would not produce any nephrocalcinosis in the majority of the animals A few animals showed the very beginning of calcification as demonstrated by small flecks of calcification within the basement membrane of the renal tubules As the amount of parathormone was increased, more and more calcium was deposited, first still confined to the peritubular basement membrane Calcium soon appeared within the basement membrane of Bowman's capsule Finally, as the dosage reached 1600–1700 units, calcium appeared within the lumen of the tubules At this point there was so much calcification that it was no longer possible to determine its exact morphological location The peritubular and intratubular deposition of calcium are demonstrated in figure 1

With 1600–1800 units of parathormone calcification was also observed beneath the splenic capsule, in the basement membrane of the large and small arteries and arterioles, under the endocardium and also in the connective tissue of the stomach (fig 2) No calcification was found other than in the connective tissue ground substance of these organs and structures Although all experimental animals reacted in a similar manner to low doses of parathormone, the quantity of calcification produced by larger, but identical amounts, of parathormone varied considerably among different series of rats This inconsistency was not demonstrated among rats received in the same shipment, but was frequently observed when one shipment was compared to another Since all the animals received were of the same strain, age, sex and approximate size, there was no obvious explanation of this phenomenon In order to insure meaningful results, a control group from the same shipment was included in every experiment It is interesting that although there were different reactions to parathormone from group to group, the serum calcium levels were always quite similar Only one lot of Lilly's parathyroid extract was used for the entire experiment

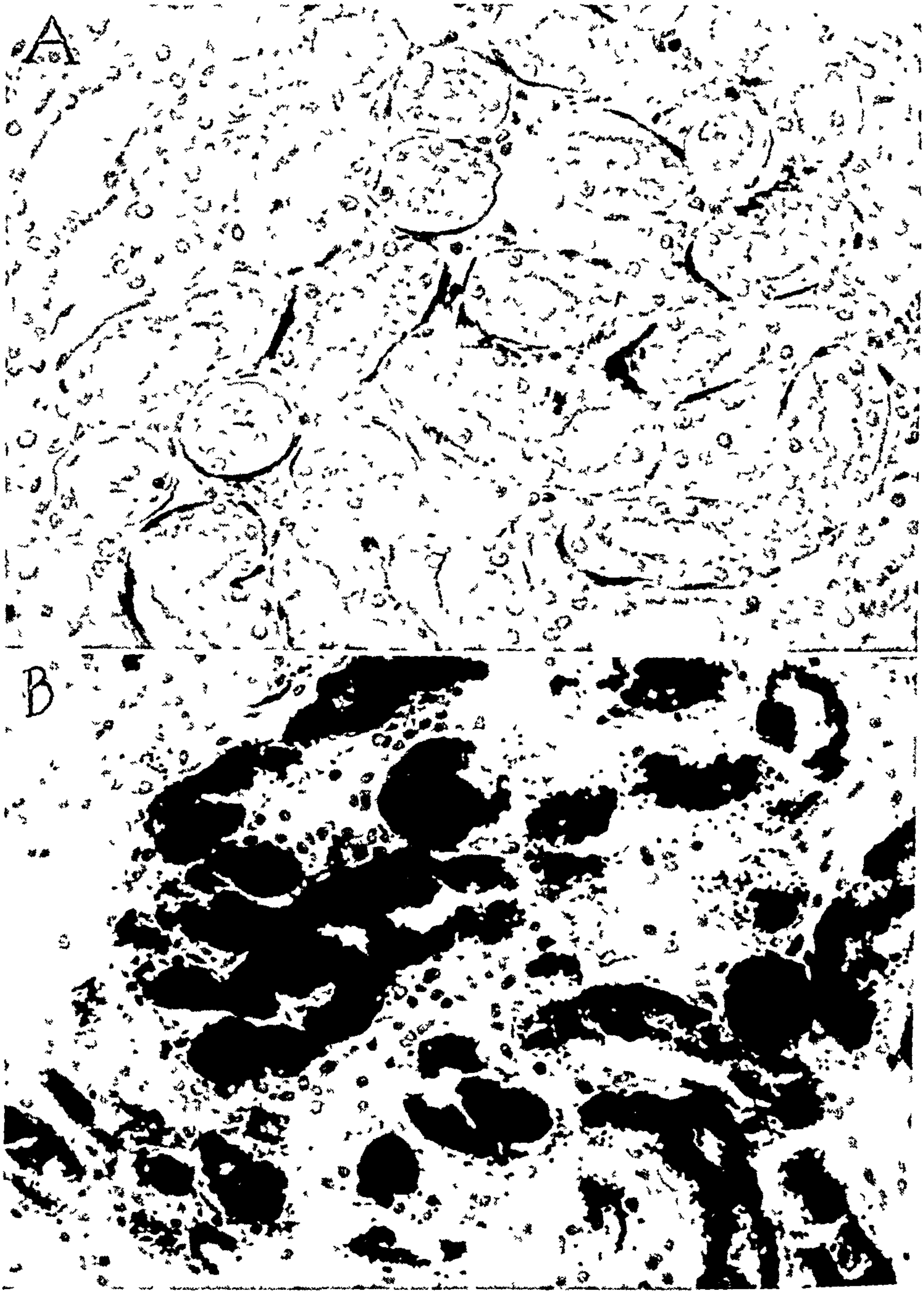

FIG 1 *A*, nephrocalcinosis produced by administration of 1000 units of parathormone Observe calcification appears first only in connective tissue basement membrane of renal tubules × 460 *B*, effect of increasing dosage to 1625 Calcification appears in basement membrane and also within tubules in this group of rats × 460

II. *Nephrocalcinosis and alteration of ground substance.* The administration of toluidine blue to rats receiving parathormone greatly augmented nephrocalcinosis and calcification occurring in the connective tissue as compared to control animals. Animals given 1,000 units of parathormone rarely developed any renal

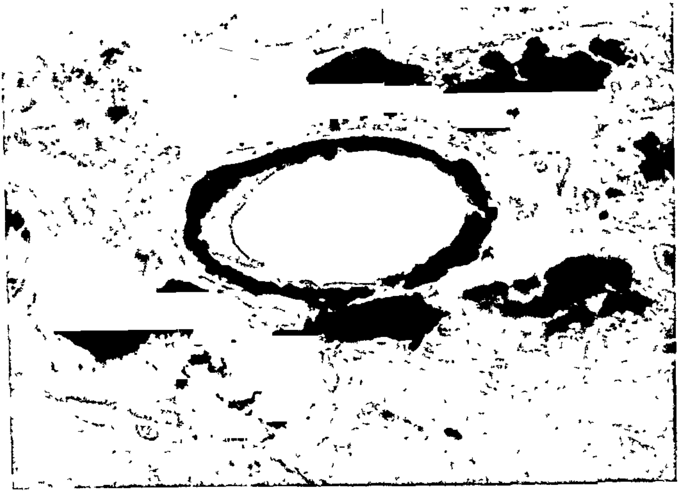

FIG. 2. Demonstration of metastatic calcification associated with 1,625 units of parathormone. Calcification is selectively deposited in basement membrane of blood vessel and in other connective tissue surrounding vessel. × 900

tubular calcification. The concurrent administration of toluidine blue with this same quantity of parathormone, however, produced extensive calcification. In these animals an ineffective amount of parathormone had become effective by use of toluidine blue. Figure 3 demonstrates the markedly increased calcification produced by the concurrent use of toluidine blue with 1,625 units of parathormone, as compared to control animals receiving only this same quantity of the hormone. These results are scored in table 1.

The administration of desoxycorticosterone acetate (DOCA) to animals that were receiving parathormone almost completely inhibited nephrocalcinosis. The animals were sacrificed at the height of the parathormone induced hypercalcemia, yet only one animal receiving DOCA showed any appreciable metastatic calcification. The total serum calcium, plasma protein, and ionized calcium values in the two groups were identical. These results are presented in table 2.

Calcification produced by parathormone was much more extensive in the hypertrophied kidney than in the normal kidney (fig. 4). This was found to be true at high and low dosage levels of the hormone. The nephrocalcinosis observed with 1,000 units was greatly in excess of that produced in a normal rat given the same amount of parathormone. This effect is exaggerated using 1,625 units of the hormone. The results of the administration of parathormone to normal animals and to rats with hypertrophied kidneys are presented in table 3.

III. *Effect of increased serum calcium on renal calcification.* Serum calcium concentration in normal, untreated rats was 11.7 mg. per cent. Animals receiving 1,000 units of parathormone had a serum calcium level of approximately 13 mg. per cent. To determine whether the renal calcification observed with parathor-

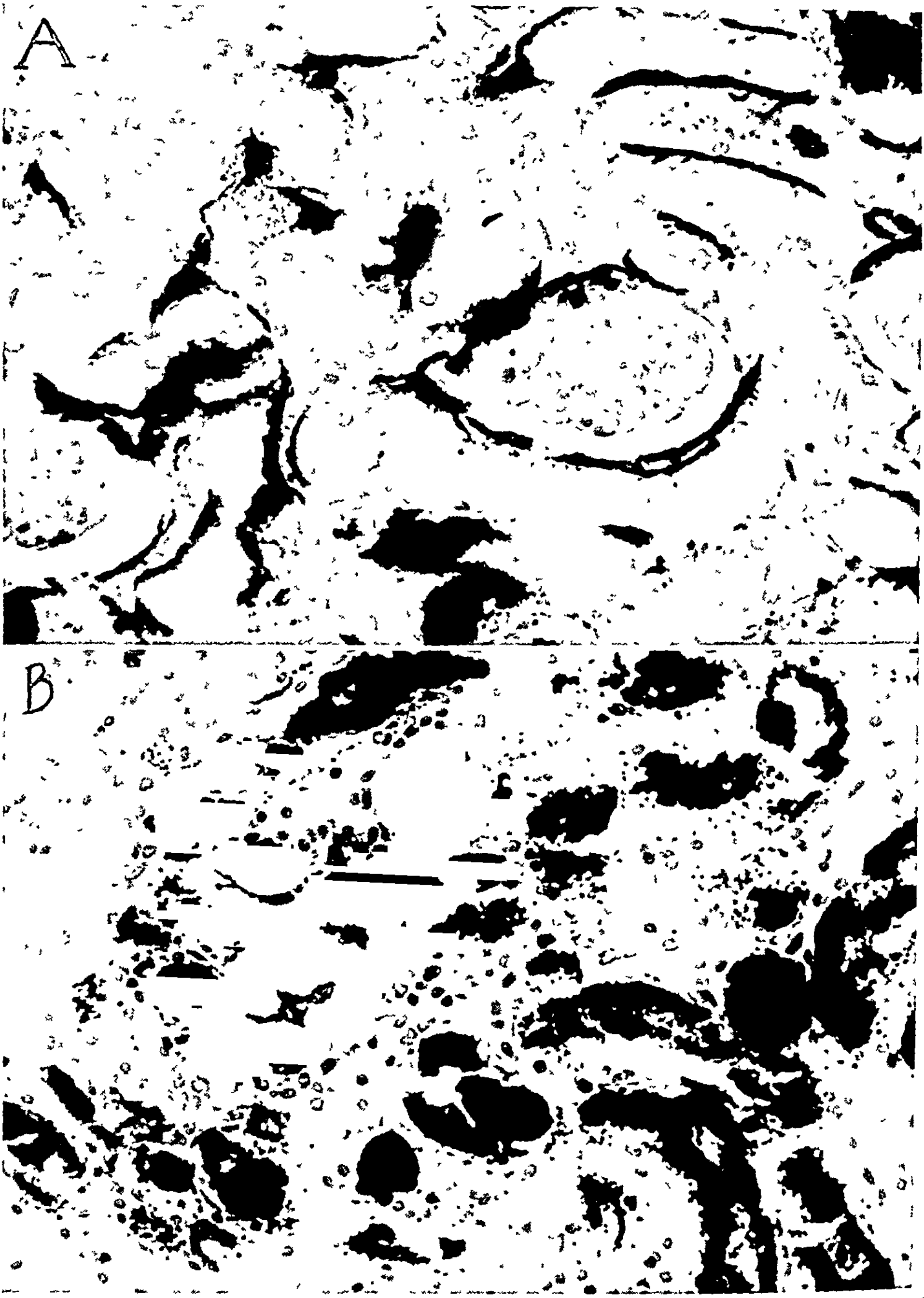

Fig. 3. *A*, calcification in basement membrane of renal tubules in rat produced by 1625 units of parathormone. × 460. *B*, augmentation of parathormone effect (1625 units) by concurrent administration of toluidine blue. × 460

mone was a result of the increased serum calcium levels, the next experiment was designed to determine whether a comparable amount of calcium given directly might also produce nephrocalcinosis. One gram of dibasic calcium phosphate that was implanted intramuscularly in 10 rats was found to have been completely absorbed at the end of a 2-week period. The serum calcium in these animals was

TABLE 1 *Influence of toluidine blue on metastatic calcification*

NO OF ANIMALS	TREATMENT	DURATION	DEGREE OF CALCIFICATION WITHIN EACH EXPERIMENT			
			0	+	++	+++
15	Parathormone (1625) units	14 days	8	4	1	2
5	Parathormone (1625 units) and 0 9 per cent saline	14 days	4	1	0	0
15	Parathormone (1625 units) and toluidine blue	14 days	0	0	5	10
8	Toluidine blue	14 days	8	0	0	0

TABLE 2 *Influence of DOCA on metastatic calcification*

NO OF ANIMALS	TREATMENT	DURATION	DEGREE OF CALCIFICATION WITHIN EACH EXPERIMENT			
			0	+	++	+++
5	Parathormone Total dosage 1625 U	14 days	0	0	1	4
5	Parathormone Total dosage 1625 U	14 days	3	1	0	1

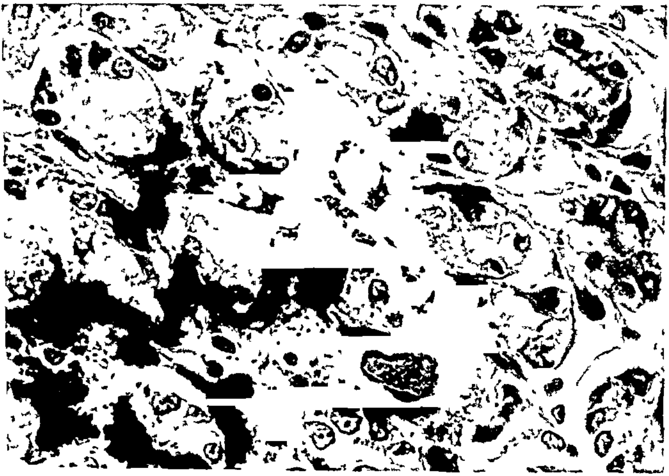

FIG 4 Hypertrophied kidney produced by contralateral nephrectomy Marked increase in parathyroid effect (1,000 units) resulting from alteration in renal connective tissue ground substance Control animals demonstrated calcification only in basement membrane of tubules × 980

approximately 13 to 13 8 mg per cent Calcium gluconate injected intraperitoneally over a 2-week period in one group of rats, and over a 4-week period in another group of rats, increased the serum calcium concentration to about 13 4 mg per cent In both instances the serum calcium levels were comparable or

TABLE 3. *Effect of rapid growth on metastatic calcification*

NO. OF ANIMALS	TREATMENT	DURATION	DEGREE OF CALCIFICATION WITHIN EACH EXPERIMENT			
			0	+	++	+++
10	Normal rat kidney Total dosage 1625 U parathormone	14 days	4	6	0	0
10	Hypertrophied rat kidney Total dosage 1625 U parathormone	14 days	0	1	2	7
10	Normal rat kidney Total dosage 1000 U parathormone	14 days	8	2	0	0
10	Hypertrophied rat kidney Total dosage 1000 U parathormone	14 days	0	4	6	0

TABLE 4. *Effect of hypercalcemia on renal calcification*

NO. OF ANIMALS	TREATMENT	DURATION	SERUM CALCIUM (MG. %)		DEGREE OF CALCIFICATION WITHIN EACH EXPERIMENT			
			Range	Mean	0	+	++	+++
7	Control		11.1–12.6	11.7	7	0	0	0
8	Parathormone Total dosage 1625 U.	13 days	12.6–14.2	13.6	0	1	2	5
10	Dibasic calcium phosphate Total dosage 1 gm.	13 days	13.0–13.8	13.4	10	0	0	0
10	Calcium gluconate Total dosage 206.25 mg.	13 days	12.8–13.6	13.2	10	0	0	0
10	Calcium gluconate Total dosage 1775 mg.	28 days	13.0–14.0	13.6	10	0	0	0

increased as compared to those obtained by giving parathormone. A total of 30 rats were used to test the effect of the direct administration of calcium on the production of calcification. All of the animals receiving parathormone showed extensive metastatic calcification. No calcium was deposited in any of the animals receiving calcium directly either at 14 or 28 days. These results are summarized in table 4. It was considered unnecessary to determine the levels of ionized calcium on all of these animals. The results indicate an identical increase in the ionized fraction.

DISCUSSION

It has been demonstrated that the minimal effective amount of parathormone necessary to produce nephrocalcinosis is usually slightly in excess of 1,000 units administered over a two-week period. A total dosage of 1,300 and 1,625 units of parathormone demonstrate progressively increasing amounts of calcification within the kidney. All of the calcification produced by parathormone occurred first within the ground tissue matrix. Any increase or spread in nephrocalcinosis is an extension or result of calcification developing first in this area. With large amounts of parathormone, calcification also becomes intratubular. This effect on the ground substance is in a sense metastatic in that the connective tissue matrix elsewhere in the rat demonstrates the same calcification It was observed in the arteries, heart, spleen, and stomach It has been possible by measuring the degree of calcification produced, to confirm a recent hypothesis of Milton Engel that parathormone has a direct action on ground substance This finding is also an extension of Albright's observation that parathormone has a direct action on renal tubules Reports in the literature, and the observations now presented, indicate that parathormone induced calcification begins and is progressive within the connective tissue It would appear that this calcification within the connective tissue ground substance is not simply fortuitous, but that the state of the connective tissue is intimately concerned in the process of calcification

A simple increase in serum calcium, equal to that observed with administration of parathormone, by the administration of dibasic calcium phosphate or calcium gluconate failed to produce nephrocalcinosis in the 30 animals studied As a result of this experiment it would appear questionable whether the metastatic calcification induced by parathormone is completely a result of its effect on the mobilization of calcium Parathormone produces increased serum calcium, but increased serum calcium does not necessarily indicate nephrocalcinosis These data support the theory of Milton Engel, that the hormone depolymerizes ground substance and thereby increases calcifiability

An attempt has been made to indicate that the state of the connective tissue ground substance is intimately concerned in determination of where, when and to what degree, calcification will occur This has not been previously reported To demonstrate this phenomenon, three methods were employed to show that if the state of the connective tissue matrix is altered, the ability of that tissue to undergo calcification is also changed

Toluidine blue was administered as it is known to bind with free sulfate groups of the acid mucopolysaccharide in the ground substance This dye has been shown to inhibit the binding of calcium in slices of rachitic rat cartilage It might be assumed that an alteration in binding capacity of the matrix by tying up the free reactive groups with toluidine blue, might inhibit subsequent calcification associated with parathormone administration The exact converse proved to be true in the experiments now presented An ineffective amount of parathormone produced calcification of the ground substance of the kidney and other structures when administered in conjunction with toluidine blue The parathormone effect was greatly augmented by current use of toluidine blue A possible explanation for this reaction appears to be that toluidine blue is an anionic dye and binds to different loci on the ground substance than the cationic calcium As a result, no competitive binding to the matrix would be expected The binding of toluidine blue to the chrondroitin sulfate of the ground substance apparently alters or depolymerizes the structure of the glycoprotein, enabling an effective amount of parathormone to produce greater calcification than is possible with the hormone alone It also permits an ineffective amount of parathormone to produce nephrocalcinosis and metastatic calcification Data to be reported later, indicate that this augmentation of calcification by toluidine blue may be effectively blocked by the concurrent administration of heparin This antagonism of heparin to toluidine blue was first shown by Allen and is quantitatively expressed in a ratio of approximately 200 micrograms of toluidine blue to 90 micrograms of heparin.

Selye and others have shown that DOCA is capable of increasing the normal inflammatory response to a local irritant. The effect of DOCA could be explained on the basis of its ability to increase the polymerization of the ground substance. If this were true, and if polymerization of the ground substance renders the tissue less likely to become calcified, DOCA should inhibit parathormone induced calcification. The results indicate that DOCA does inhibit metastatic calcification. In 80 per cent of the animals receiving DOCA and parathormone that were sacrificed at the height of the parathormone induced hypercalcemia, there was no appreciable calcification. All of the animals receiving the same amount of parathormone, but not receiving DOCA, showed extensive metastatic calcification. In addition the total plasma proteins, total serum calcium and ionized calcium levels were identical in the two groups. Admittedly, the group of animals studied is small and there is no conclusive evidence that DOCA does polymerize the ground substance. It is also true that DOCA is capable of producing widespread metabolic changes that may influence the observed results. None the less, as a result of these experiments there is no doubt that DOCA does alter tissue calcifiability without altering either total or ionized calcium levels. Since the effect of DOCA was predicted on the basis that it would polymerize ground substance, it is felt that it is highly suggestive evidence for the thesis presented.

The third method now reported for altering the connective tissue ground substance is compensatory renal hypertrophy. Gersh has pointed out that the ground substance in the region of certain rapidly growing tumors becomes depolymerized. It might be expected that a similar phenomenon would occur in any rapidly growing area. Aterman has shown that in regenerating rat liver there is a marked depolymerization during the stage of rapid growth. It is known that healing wounds, arthritis, tuberculosis, hyperplasia and hypertrophy are associated with an increase in tissue glycoproteins. Contralateral nephrectomy produces a marked hyperplasia or hypertrophy of the contralateral rat kidney. This method of inducing rapid growth seemed most desirable as it precluded any mechanical interference with the tissue being investigated. If the assumption that a depolymerization of the ground substance increases tissue calcifiability is correct, and if in fact there is a depolymerization in the hypertrophied kidney, it would be expected that there would be an increase in the amount of calcium laid down in the hypertrophied kidney. In the present experiments, it was obvious even grossly, that the hypertrophied kidney had reacted differently than a normal kidney to the same amount of parathormone. There was considerably more calcium deposited in the hypertrophied kidney of rats receiving 1,625 units of parathormone than in normal animals receiving an identical amount of the hormone. The results were more striking in the animals receiving 1,000 units of parathormone. Normal animals on this regimen showed no appreciable calcification, as contrasted to the extensive calcium deposition in the hypertrophied kidneys of rats receiving an equal quantity of parathormone.

The data now reported confirm the impression that alterations in the state of the connective tissue is a vital factor concerned in pathological calcification Additional experiments are in progress that indicate the same results are obtained with alterations of the ground substance by experimental renal trauma, induced pyelonephritis and renal tubular injury produced by hydronephrosis secondary to incomplete ureteral ligation In addition, other methods of producing renal calcification by means of radiated ergosterol and also oxamide are underway to determine whether the same alterations of ground substance always precede calcification produced by other causes

From the clinical standpoint, Anderson has reported that in patients with hyperparathyroidism, the calcification is identified by an interstitial degenerative effect that precedes deposition of calcium

It is also of considerable interest that the concept and supporting evidence now presented concerning calcifiability and the state of the connective tissue ground substance was tacitly implied by Randall many years ago Randall believed that *a primary renal calculus is only a symptom* He presented evidence that renal calculi always originate as a slow crystallization of urinary salts which depend on calcification in a pathological disease condition of the kidney Randall observed that papillary changes frequently preceded the development of primary renal calculi, and acts as the initiating lesion upon which urinary salts crystallize Photomicrographs supporting his conclusions demonstrate that in addition to the papillary plaques described, that there is also calcification in the basement membrane (ground substance) of the renal tubules We have observed that experimental renal trauma alters the local state of the ground substance and increases *calcifiability* of that area This evidence confirms the extensive clinical investigations of Randall

Experimentally, other factors also produce depolymerized renal ground substance and affect susceptibility for calcification chronic or recurrent renal infections with gram negative organisms, obstructive uropathy with secondary renal tubular damage produced by incomplete ureteral ligation, simulation of the metabolic disease gout by continued administration of uric acid, hormonal imbalances such as hyperparathyroidism or administration of cortisone, and finally prolonged dehydration All of these experimental procedures have their counterpart in renal calcification as observed in patients In addition all of these procedures have a common biochemical effect in that by changing the chemical state of the renal ground substance they increase renal calcifiability.

CONCLUSION

Evidence has been presented that the calcification induced by parathormone may not be entirely due to its ability to raise serum calcium levels, and that the state of the connective tissue is vitally concerned with calcifiability Altering the state of the ground tissue by means of toluidine blue, DOCA or renal hypertrophy increases or decreases nephrocalcinosis

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A PELVIC FLAP OPERATION FOR CERTAIN TYPES OF URETEROPELVIC OBSTRUCTION OBSERVATIONS AFTER TWO YEARS' EXPERIENCE

ORMOND S CULP AND JAMES H DEWEERD
Section of Urology, Mayo Clinic, Rochester, Minnesota

None of the numerous operations advocated for correction of ureteropelvic obstruction has been ideal for all types of cases We have had superb results after employing the well known Foley Y-plasty[1] but it was designed for and should be confined to hydronephrosis with high insertion of the ureter on an extrarenal pelvis When utilized properly this ingenious procedure provides a new, funnel-shaped, dependent, ureteropelvic juncture of good caliber

Many obstructed ureteropelvic junctures, however, already occupy a dependent position, as shown in figure 1*a* Occasionally there is more extensive constriction of the ureter as seen in figure 1*b* The Y V method of repair is not feasible for obvious reasons Dissatisfaction with other plastic procedures in cases of this type prompted an attempt to devise a simple technique that might incorporate some of the commendable features of the three dimensional Foley operation

In 1951 we published a preliminary report[2] of a pelvic flap operation which appeared to have achieved this objective The cardinal steps in this method are illustrated in figure 2

TECHNIQUE

Converging incisions from a broad, slightly oblique base adjacent to the original ureteropelvic juncture are joined after following the spherical contour of the dilated renal pelvis for sufficient distance to assure a flap longer than the constricted segment of ureter (fig 2*a*)

Since the enlarged pelvis is much like a ball poised on the end of a narrow spindle, the flap falls parallel to the upper end of the ureter without angulation (fig 2*b*) The ureter is incised beyond the lower limit of the constriction (fig 2*b*) and corresponding edges of split ureter and pelvic flap are united with interrupted sutures of size 000 chromic catgut (fig 2*b* and *c*)

A splinting tube of appropriate caliber and a separate nephrostomy tube are inserted through one of the calyces in the lower pole after which the splint is passed down the ureter for several centimeters (fig 2*c*) Remaining edges of flap and ureter are sutured over the splint and the defect in the pelvis is closed (fig 2*d*)

Read at annual meeting, American Urological Association, St Louis, Mo , May 14, 1953

Note by editor The authors' exhibit on the pelvic flap operation was awarded first prize at the same meeting

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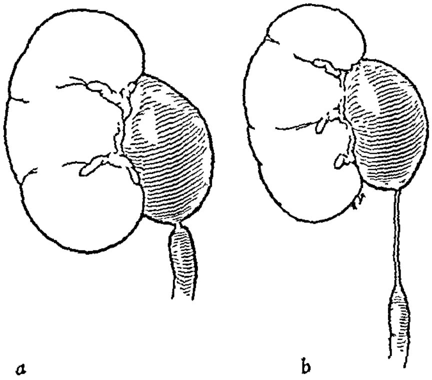
[1] Foley F E B A new plastic operation for stricture at the ureteropelvic junction, report of 20 operations J Urol 38 643-672 1937

[2] Culp O S and DeWeerd, J H A pelvic flap operation for certain types of uretero pelvic obstruction Preliminary report Proc Staff Meet , Mayo Clin , 26 483-488, 1951



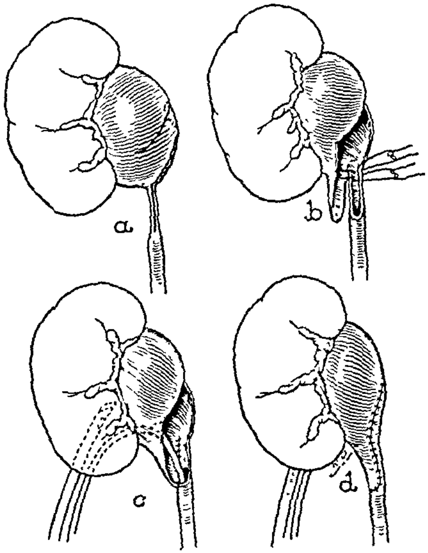


FIG. 1 FIG. 2

FIG. 1. *a*, Typical dependent ureteropelvic obstruction. *b*, More extensive constriction in upper portion of ureter.

FIG. 2. *a*, Location of incisions to create pelvic flap and to open constricted segment of ureter. *b*, Anatomic relationship of flap and open ureter; adjacent edges are joined by sutures of 000 chromic catgut. *c*, Nephrostomy tube and ureteral splint inserted through lower calyx after one edge of flap has been attached to split ureter. *d*, Flap sutured to other edge of split ureter over the splint, and defect in pelvis closed.

We usually remove the ureteral splint at the end of two weeks and take out the nephrostomy tube twenty-four to forty-eight hours later.

APPLICATION

This operation has been used only when the obstructed ureteropelvic juncture has been dependent. Length of the flaps varied from 2 to 8 cm. In 2 instances it was impossible to construct a flap long enough to compensate for unusually extensive ureteral narrowing and the flap operation was combined with the Davis intubation ureterotomy[3] (fig. 3). Successful use of this combination is demonstrated by figure 4*a* and *b*.

From May 7, 1951, to October 17, 1952, we performed 28 pelvic flap operations. One woman, aged 40 years, died suddenly and unexpectedly 24 hours after operation. Postmortem examination revealed pulmonary and cerebral edema, grade 3. The operative site presented nothing remarkable and the specific type of operation played no part in her untimely death.

The other 27 cases have permitted critical evaluation of results six to twenty-four months after operation. Eighteen of these patients had their operations more than one year ago.

Females outnumbered the males 17 to 10. The right ureteropelvic juncture was repaired in 15 cases and the left required correction in the other 12. Ages of the patients varied from 4 to 52 years with an average of 30.5 years. Only 7 patients were more than 40 years of age.

[3] Davis, D. M.: Intubated ureterotomy; a new operation for ureteral and ureteropelvic stricture. Surg., Gynec. & Obst., **76**: 513–523, 1943.

RESULTS

In most instances the final result was especially gratifying. For example, a young man, aged 16 years, had pain in the right flank for six weeks. The excretory urogram showed right hydronephrosis (fig. 5*a*). All discomfort disappeared after operation, and an excretory urogram 18 months later appears normal (fig. 5*b*).

A woman, aged 26 years, had pain in the right flank for 1 year. The right kidney was hydronephrotic and emptied poorly (fig. 6*a*). Aberrant vessels crossing the original ureteropelvic juncture were preserved. All pain subsided after the plastic repair. An excretory urogram 8 months later appears normal (fig. 6*b*).

Adequate evaluation of more complex situations can be especially difficult. When there has been long-standing hydronephrosis, some degree of pyelocaliecta-

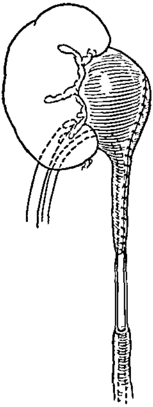


FIG. 3. Flap operation combined with intubation ureterotomy because of extremely long ureteral stricture.

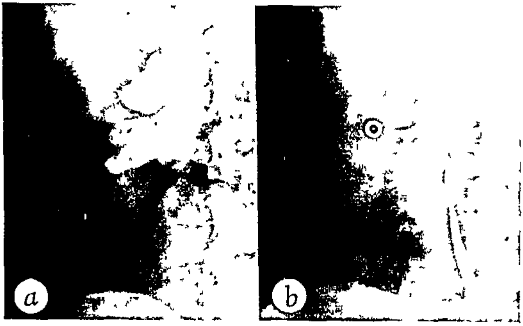


FIG. 4. *a*, Preoperative excretory urogram *b*, Retrograde pyelogram 2 months after combined flap operation and intubation ureterotomy.

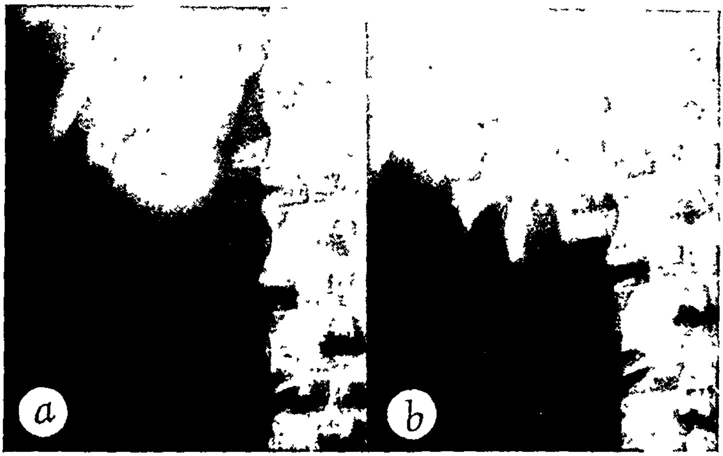


FIG. 5. *a*, Preoperative excretory urogram. *b*, Excretory urogram 18 months after flap operation.

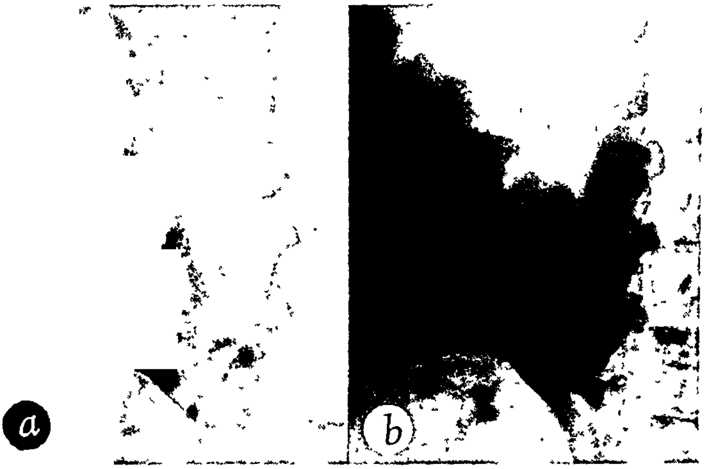


FIG. 6. *a*, Preoperative 10-minute delayed retrograde pyelogram. *b*, Excretory urogram 8 months after flap operation.

sis may persist because of permanent cortical damage. The general health of patients and the elimination of renal infection are considered more significant than the pyelographic appearance of the kidney.

In many cases it was possible to compare postoperative delayed retrograde pyelograms with those made before operation and to note the more efficient emptying after operation. But such studies were not indicated or justified in every case. It is noteworthy that calculi had developed in the obstructed kidneys of 6 patients and that there have been no recurrences.

Preoperative investigations showed that all of our 27 patients had some degree of hydronephrosis, 25 had pain on the same side and 20 had infection in the affected kidney. An analysis was made of these three manifestations *after* operation in each case, and the results are summarized in table 1. Only 2 patients continued to have their discomfort. The same 2 remained infected and the hydronephrosis failed to improve. Four other patients still had infected urine but all

TABLE 1 *Analysis of significant preoperative and postoperative data in 27 cases*

	PRESENT BEFORE OPERATION	AFTER OPERATION		
		Absent	Improved	Unimproved
Pain	25	23	0	2
Infection	20	14	4	2
Dilatation	27	17	8	2

TABLE 2 *Results of 27 pelvic flap operations performed from May 7, 1951, to October 17, 1952*

MONTHS SINCE OPERATION	CASES	RESULT		
		Well	Improved	Unimproved
6–12	9	4	3	2
13–18	6	5	1	0
19–24	12	8	4	0
Total	27	17	8	2

chills and fever had subsided The urine of the remaining 14 who had infection preoperatively became sterile after operation and appropriate chemotherapy, and there has been no recurrence of the infection There were many degrees of initial hydronephrosis In 17 cases it was absent or negligible postoperatively, while in 8 there was only marked reduction in size

Each patient was appraised in terms of composite postoperative findings, general physical condition and probable prognosis Three categories have been employed as seen in table 2 "Well" patients are those who have essentially normal-appearing pyelograms, no pain and no infection Seventeen qualified for this group despite the rigid standards

"Improved" patients are those who have had truly significant alteration of their preoperative status but who still harbor some degree of infection or pyelocaliectasis The 8 patients in this group, however, include some with the most dramatic results For example, a woman, aged 47 years, had far-advanced bilateral hydronephrosis and a blood urea concentration of 90 mg per 100 cc Permanent nephrostomy seemed inevitable but after a flap operation the right kidney emptied astonishingly well and the nephrostomy tube was removed The concentration of blood urea has dropped to 32 mg even though the renal pelves remain huge Her general health is so much better that she refuses a similar procedure on the left kidney The operation undoubtedly was successful but the patient can hardly be considered entirely well

Two cases represented frank failures, and secondary nephrectomy was required

COMPLICATIONS

Severe and extensive ureteritis and periureteritis which resulted in ureteral occlusion caused the 2 failures that occurred

A third patient had an intrarenal hemorrhage on the tenth postoperative day Blood clots obstructed the nephrostomy tube, and a urinary fistula developed.

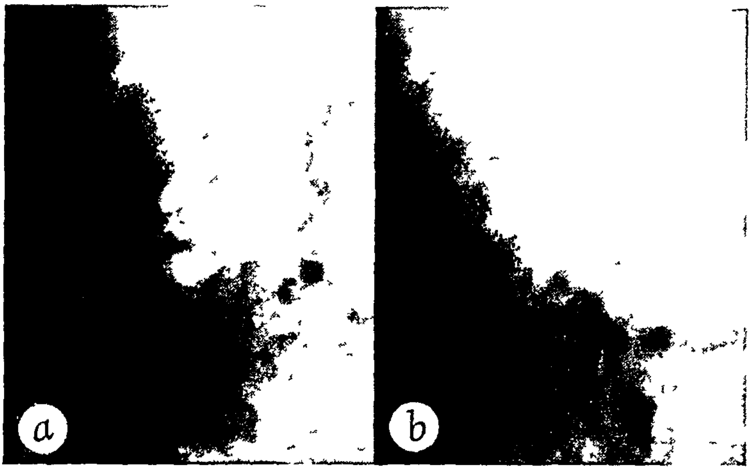


FIG 7. *a*, Preoperative excretory urogram. *b*, Excretory urogram 7 months after flap operation.

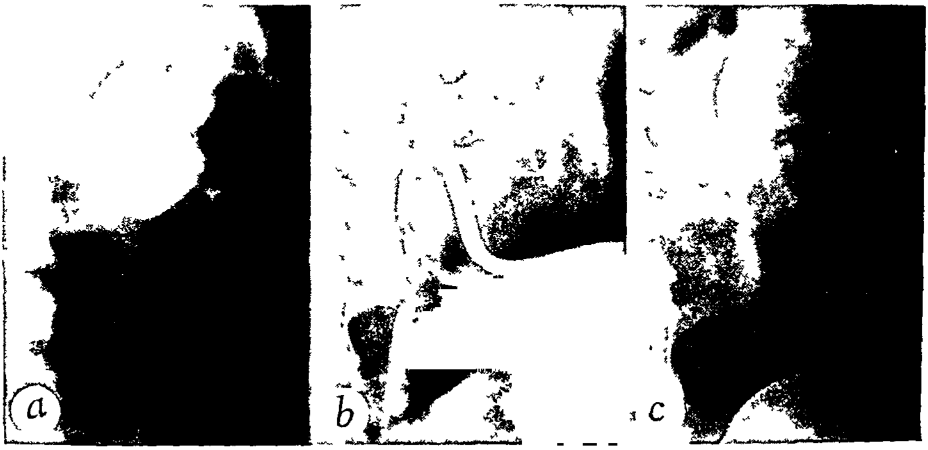


FIG 8 *a*, Preoperative 25-minute delayed retrograde pyelogram *b*, Pyelogram through nephrostomy tube on fourteenth postoperative day *c*, Excretory urogram 18 months after flap operation

When the kidney was re-explored, it was discovered that one suture line along the flap was wide open The flap and ureter were rejoined over a splint, and the final result was most satisfactory as seen in figure 7.

One patient had pain and fever after returning home, and urine began to drain through the incision. Indwelling ureteral catheter drainage instituted by her home urologist afforded timely relief and complete healing. A recent excretory urogram shows an excellent result.

Two patients developed phlebothrombosis in one of the lower extremities but both recovered promptly after anticoagulant therapy.

There have been questions regarding possible avascular necrosis at the tip of the pelvic flap. It has been our policy to make pyelograms through the nephrostomy tube before the latter is removed. Four patients showed some degree of leakage from the operative site at the end of two weeks. Figure 8 illustrates 1 of these The extravasation was ignored and it did not jeopardize the final result as can be seen in figure 8c The other 3 patients had equally gratifying results

Most patients were dismissed from the hospital on the sixteenth to eighteenth postoperative day and a few left on the seventh to tenth day after operation with the nephrostomy tube attached to a suitable receptacle

SUMMARY

By redeploying a flap of tissue from the renal pelvis it is possible to correct ureteropelvic obstruction when the juncture has a dependent position instead of a high insertion The size of the flap can be increased to repair long constrictions in the upper segment of the ureter

The operation is simple, does not require excessive hospitalization and is fraught with no more hazards than other types of plastic operations on the pelvis and ureter

Twenty seven patients treated by this method have been followed for six to twenty-four months after operation Seventeen now have an essentially normal kidney, 8 others have shown marked improvement and 2 have had complete failure necessitating secondary nephrectomy

When adapted to properly selected cases, the operation seems to have sufficient merit to justify its continued use

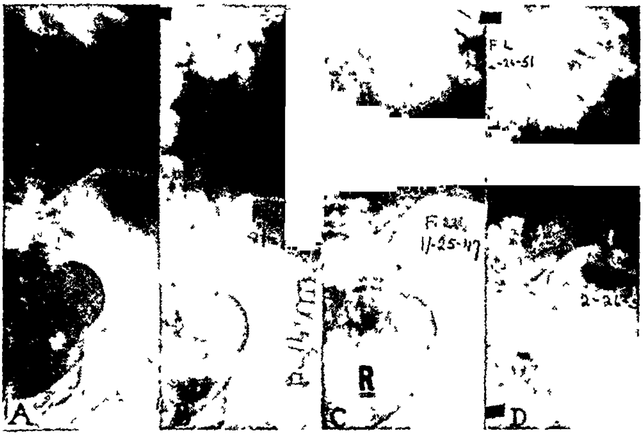


FIG. 1. Case 1. *A*, large shadow in left bony pelvis. *B*, shadow is calculus in lower left ureter causing sausage dilatation of entire ureter and hydronephrosis of left kidney. *C*, three months postoperative Lower ureter still shows some dilatation. *D*, 3½ years postoperative. Pelvis, calyces and ureter have returned to normal.

Morphine is still the best drug for the control of renal colic. Experimentally it has been shown that morphine increases peristalsis of the ureter and temporarily, an exacerbation of the pain. The final action of the drug, however, is cerebral. The patient falls asleep and, while asleep, the ureter relaxes and dilates to permit urine to pass beyond the stone. Antispasmodics, such as Trasentine, Prostigmin, Depropanex, Octin, Banthine and a host of other drugs are too uncertain and too slow in their action. The dosage of morphine should be 30 mg. (gr. ½) subcutaneously. This drug is most efficacious when combined with atropine.

Many urologists recommend surgery for repeated renal colic attacks. They maintain that their patients often have prolonged and frequent episodes of pain which no drug seems to control. The author has not encountered too many instances of uncontrollable pain for ureteral calculus. When his patient has not been helped by morphine mg. 30, this dosage is repeated within two hours, usually with excellent results. The symptom of pain alone should never influence or justify the surgeon to operate.

PROCEDURES EMPLOYED TO ASSIST RADIABLE STONES IN THE URETER TO PASS SPONTANEOUSLY

A scout x-ray film of the abdomen is taken of the patient suspected of having a ureteral calculus. If no radiable shadows are visualized, careful scrutiny is given the bony structures of the sacrum and ilium. Often, a stone in this area is obscured by the greater density of the bone.

Stones in lower ureter. The diagnosis of calculus is verified by passing up the ureter a No. 5 ureteral catheter, usually wax-tipped, and a plain x-ray taken with the cystoscope still in the patient. The catheter may have been stopped at the site of the stone or it may have passed beyond it, showing the catheter in contact with the calculus. A second or even third No. 5 catheter, usually of the spiral variety, is introduced alongside the first catheter. The cystoscope is removed, urine collected, functional tests carried out, followed by pyelograms, ureterograms and retention films If more than one catheter has been passed up the ureter, the catheters are often twisted before removal in the hope that the stone will be dislodged or possibly withdrawn in the meshes of the catheters This procedure of introducing one or more ureteral catheters is repeated every 2 or 3 weeks If at the end of 3 months, the stone is still to be found in the ureter, the above procedure is carried out at longer intervals, usually from 4 to 12 week periods until the stone is finally passed spontaneously At times, the catheter or catheters are not removed but left in for 24 to 48 hours Retention catheters left in for longer periods may result in renal infection, in spite of antibiotic therapy, and should therefore be avoided

Occasionally on cystoscopic examination, a large stone is observed occupying the ureteral orifice If it cannot be dislodged with a ureteral catheter, fulguration of the superior lip of the ureteral orifice, rather than ureteral meatotomy, is carried out The stone will drop into the bladder in a few days and be passed

The term ureteral dilatation has been purposely omitted It is the author's opinion that the mere introduction of catheters does not dilate a muscular tube such as the ureter sufficiently to be of any real benefit The ureter must certainly rebound to its original caliber when the catheters are removed The purpose of the passage of catheters is to change the axis of a stone or to budge it even a trifle so that a quiescent stone may initiate movement to terminate in spontaneous expulsion from the ureter If one wants genuine dilatation, indwelling catheters will accomplish this end successfully

The Dourmashkin bag has been employed but not with too certain success The loop catheter has been tried, but no ureteral calculus has ever been snared The use of wire baskets often results in chills and fever and occasionally in rupture of the ureter with urinary extravasation and has been discontinued in favor of methods producing fewer complications

Stones in upper and middle ureter The diagnosis of calculi in the upper and middle ureter is usually made by excretory urography rather than by retrograde catheterization For good visualization of the pelvis, calyces and ureter, it may be necessary that x ray films be taken at the end of 45 minutes, 1 hour, 1½ hours and even 2 hours in addition to the routine 5, 15 and 30 minute exposures The delayed x ray films will often outline the entire ureter, proving that complete obstruction by the stone does not exist If one depended on routine excretory films, the visualization may often be incomplete or misleading

If the stone in the upper and middle ureter is 1½ cm or larger, it had best be removed by operation If the stone is small or medium size, a period of waiting is indulged in until it descends to a level below the crest of the ilium, preferably to the region of the sacrum or bony pelvis This may be a period of a few days to several months When the calculus begins to move from the upper ureter, it may descend very rapidly When it reaches the lower ureter, the stone is treated by the methods described under Stones In Lower Ureter If ureteral catheterization were performed with the stone in the upper and middle ureter, there would always be the possibility of pushing the stone up into the renal pelvis Such a and the opaque medium was passing around the calculus with visualization of the ureter below the stone. The calculus apparently was causing minimal obstruction. On June 26, 1947, two months later, the stone was observed in the lower ureter and it was passed spontaneously, without cystoscopic treatment, July 26, 1947, after having been lodged in the lower ureter for a period of one month.

This same patient reappeared 5 years later, January 2, 1952. A routine roentgenogram demonstrated a round shadow, measuring 5 mm. in diameter, in the right bony pelvis which proved to be a calculus in the lower right ureter on excretory urography. Fortunately, for the second time, this calculus produced very little dilatation of the ureter or renal pelvis. The patient passed this stone two weeks later, January 16, 1952, without catheters having been introduced up the solitary ureter. The urine was always uninfected.

Comment: A patient with a single kidney had stones in the ureter on two different occasions. Without ureteral catheterization, these two stones were expelled spontaneously from the ureter and the patient spared two surgical operations. Had calculous anuria occurred, indwelling catheters might have been employed or ureterotomy performed.

Case 5. A. D., a man aged 40 years, was seen in the office April 5, 1948 with a history of right renal colic. The urine showed a few red blood cells, but was negative for pus and infection. A scout x-ray film visualized two shadows, ½ cm. in diameter, on the right side, one at the lower border of third lumbar vertebra and the other in the bony pelvis. When a catheter was passed up the right ureter, the shadow in the bony pelvis was in contact with the catheter, but the second shadow was outside the ureter. On retrograde urography, a rudimentary pelvis was outlined, suggesting the possibility of duplication of pelves and ureters and the shadow in region of third lumbar vertebra as being lodged in a second ureter. The patient did not return for a full year, when on April 28, 1949, an x-ray revealed two shadows in the bony pelvis. On cystoscopy, two ureteral orifices, one above the other, were seen for the first time. A catheter was introduced up each ureter and verified the original suspicion of duplicated ureters and pelves with a calculus in each separate ureter. Cystoscopy was repeated May 12, 1949, June 2, 1949, June 23, 1949 and each time a single catheter was passed up each duplicated ureter. On July 14, 1949, two No. 5 catheters were introduced up the anterior ureteral orifice, representing the upper rudimentary pelvis. These catheters were twisted and some difficulty was encountered in removing them. When they were finally withdrawn, a calculus was found in the meshes of the twisted catheters. On August 9, 1949, the remaining stone was at a lower level and, on cystoscopy, the ureteral catheters could be only advanced up to the level of the stone. Seven days later, August 16, 1949, the patient passed his second calculus from the second duplicated ureter. The urine was uninfected at all times.

Comment: A case of unilateral duplicated pelves, ureters and ureteral orifices is presented. A calculus occupied each of the duplicated ureters. One of the stones was withdrawn in the meshes of twisted catheters and the second stone was made to pass spontaneously (figs. 4, 5 and 6).

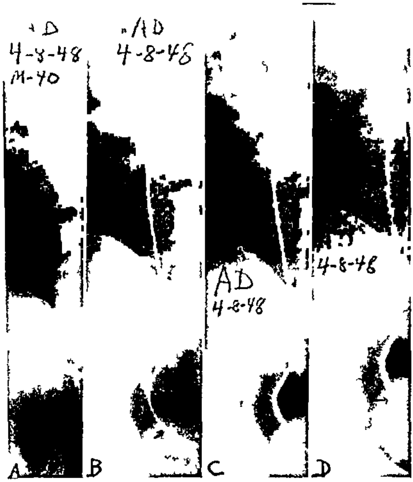


Fig 4 Case 5 A two shadows visualized one in mid right ureteral region and other in bony pelvis B catheter in contact with shadow in bony pelvis Shadow at lower edge of third lumbar vertebra outside ureter C retrograde pyelogram suggests rudimentary pelvis of double kidney and shadow medial to ureter suspicious of calculus in second ureter D, stone in lower end of ureter

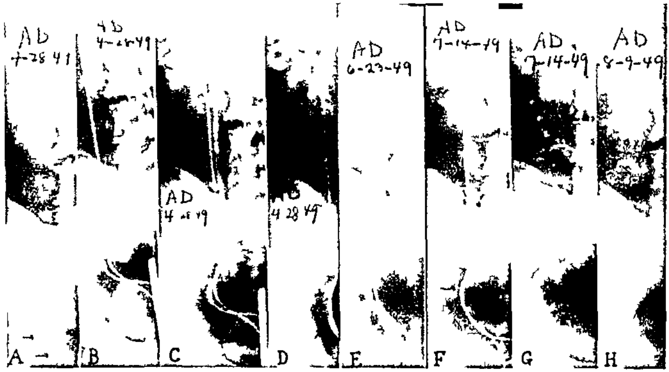


Fig 5 Case 5 A two shadows in right bony pelvis B two shadows localized to each duplicated ureter C and D duplicated renal pelvis with double ureters and calculus in each ureter E ureteral catheter in contact with stones in each duplicated ureter F, two catheters introduced up ureter of rudimentary renal pelvis (anterior ureteral orifice) G, after extracting stone by twisting catheters remaining calculus visualized in second ureter H stone at lower level in ureter draining lower pelvis (posterior ureteral orifice)

Case 6. P. R., a 40 year old man, was seen in the office September 22, 1948 with severe pains in left renal area and blood in urine. An irregular round shadow, 1 cm. in diameter, was visualized on x-ray in the left renal region. Retrograde urography revealed a relatively normal pelvis and ureter with the calculus localized to the ureteropelvic junction. A 12 minute retention film demonstrated that the renal pelvis and ureter emptied and that the calculus had been pushed into the renal pelvis and now occupied the lower pole. Ureteral catheterization would not have been carried out had the calculus been suspected of occupying the ureteropelvic junction. It was thought that it was localized to the renal pelvis and that it would not be disturbed on passage of a ureteral catheter. However, the transference of the calculus from the ureteropelvic junction to the kidney pelvis did accomplish a good purpose; it relieved the patient of pain of his ureteral colic for a long period of time. On September 30, 1948, one week later, the calculus was back to its original position at the ureteropelvic junction. Three months later, the calculus was in the midureter in the region of the fourth lumbar vertebra and 6 months later, April 8, 1949, the stone was to be found in the lower ureter. The calculus occupied the same position in the lower left ureter for almost three years, from April 1949 to March 1952. The patient consistently refused operation. This calculus passed spontaneously, March 7, 1952, 3½ years after his first consultation.

Fig. 6. Case 5. After stones were eliminated from each duplicated ureter.

In summarizing the foregoing case, the patient was cystoscoped 20 times over a period of 42 months. He had only two attacks of genuine renal colic in a period of 3½ years. The renal pelvis and ureter never showed more than first degree hydronephrosis or hydro-ureter. The urine from the left kidney was uninfected during the 3½ years the patient was under observation.

SUMMARY

A group of cases of radiable ureteral calculi expelled spontaneously from the ureter is presented. Under ordinary circumstances, these stones would have been removed by surgery, but with careful watching and nonoperative measures, they were finally passed without surgical intervention. Urinary infection and severe renal damage, factors always to be reckoned with, did not play an important role in the author's cases. Nonsurgical measures are not being suggested to replace surgery, but they should, however, be given a trial before surgery is performed.

Medical Arts Bldg., Baltimore 1, Md.

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PEDUNCULATED HEMANGIOMA OF THE URETER

M LEOPOLD BRODNY AND HYMAN HERSHMAN

From the Department of Urology, Beth Israel Hospital, Boston, Mass

Primary benign tumors of the ureter are rare, only seventy were reported in a survey of the literature up to 1945,[1] and in a more critical review in 1948[2] only 32 cases were accepted as truly benign Pathologically these growths were principally polypoid, papillomatous, granulomatous, myomatous, fibromatous, and only rarely of the vascular type This report concerns a pedunculated hemangioma of the ureter and the unusual diagnostic and surgical problems which it presented

Hemangiomas occur infrequently in the organs of the urinary tract Forty two cases of hemangiomas in the kidney were collected from the literature up to 1946 [3] Forty one cases of hemangiomas involving the bladder were reported up to 1942 [4] The vesical hemangiomas varied in size, occurred in all parts of the bladder, and sometimes cystoscopically resembled papillary epithelial tumors

The literature on primary benign ureteral tumors[1] [2] contains two direct references to hemangioma and a report of an unclassified vascular growth Herbut's textbook on *Urological Pathology*[5] notes only one case of hemangioma of the ureter Braasch and Emmett in the textbook, *Clinical Urography*[6] show an x ray of a small hemangioma of the upper end of the ureter Galbraith[10] reported a case of a pedunculated vascular tumor of the ureter which is similar to our case

CASE REPORT

I G , a white, married woman aged 49, entered the hospital complaining of dull pain on urination of 6 weeks' duration and an episode of hematuria 2 weeks previously There were no other urinary symptoms and the past history and physical examination were essentially negative Examination of the urinary sediment showed 10 to 15 red blood cells per high power field

Cystoscopy on October 4, 1952 revealed a normal bladder except for the region of the left ureteral orifice from which extruded a long, pinkish, pencil like mass, 2 5 cm in length, with an edematous tip (fig 1, *A*) During inspiration, coughing and with ureteral peristalsis, the mass elongated and projected further into the bladder With expiration and at rest, the mass retracted into the ureter until only the edematous portion was visible A No 5 ureteral catheter was easily passed up the left ureter without meeting obstruction and clear urine was ob-

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Read at meeting of New England Section, American Urological Association, Boston, Mass March 4, 1953

[1] Vest, S A J Urol , 53 97, 1945

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[4] Segal, A D and Fink, H J Urol , 47 453, 1942

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[6] Braasch, W F and Emmett, J L Clinical Urography Philadelphia W B Saunders Co , 1951, p 425

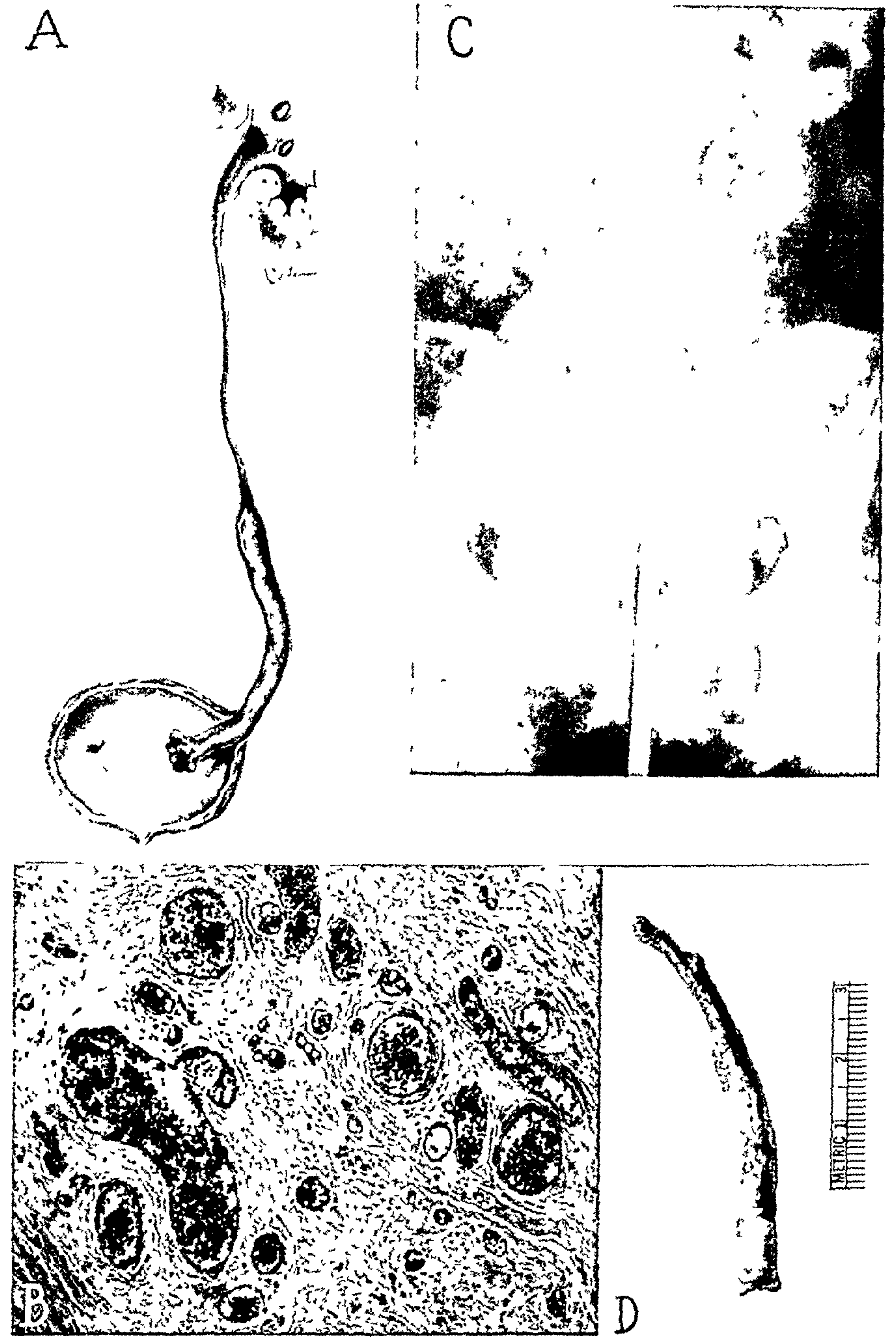

FIG. 1. *A*, composite drawing of pedunculated hemangioma of ureter based on appearance of operative specimen and on conditions observed by cystoscopy. *B*, photomicrography of biopsy specimen. Note marked vascularity. *C*, retrograde pyelogram made before cystoscopic biopsy. Filling defect present in lower end of ureter. *D*, operative specimen. Note sealed up appearance of distal end and tapering of proximal portion.

tained from the renal pelvis A left retrograde pyelogram was done The renal pelvis, calyces and upper two-thirds of the ureter were normal The distal third was dilated and there was a central cylindrical filling defect in the lumen of the entire pelvic portion of the ureter (fig 1, *C*)

A cystoscopic biopsy of the mass was performed on October 8 The No 28 Stern-McCarthy resectoscope was passed into the bladder and during inspiration, the protruding mass was cut close to the orifice in one sharp maneuver With expiration, the proximal end of the mass retracted into the ureter and did not reappear at the ureteral orifice No significant bleeding was encountered The mass was suctioned from the bladder with the Ellik evacuator The biopsy specimen measured 1 7 by 1 1 by 0 4 cm and on one end was a cystic area with a translucent covering measuring 1 2 by 0 9 by 0 4 cm The pathologic examination disclosed that the tumor was made up of a proliferation of capillaries and cavernous-like spaces, filled with blood and surrounded by fibrous reaction There was a flattened endothelium lining each blood space The pathologic diagnosis was polypoid hemangioma of the ureter (fig 1, *B*)

An excretory urogram revealed normal function on both sides and the tubular defect still present in the lower third of the left ureter

A left ureterotomy was performed under spinal anesthesia on October 15 The classical Gibson incision for exposing the lower end of the ureter was made The ureter from the brim of the pelvis to the bladder was three times its normal caliber, and there was a sharp demarcation between the upper normal and the lower dilated section (fig 1, *A*) The normal ureter just proximal to the dilatation was mobilized and a longitudinal incision 2 cm in length was made into its lumen The incision was extended for 1 cm distally An elongated mass was observed lying in the dilated lumen This was slowly teased proximally and delivered without difficulty through the ureteral incision The distal portion of the ureter almost immediately contracted to its normal caliber The base of the tumor was attached by a narrow pedicle to the lateral wall of the ureter This was generously excised by an elliptical incision well outside the origin of the stalk and the mass was removed The incision in the ureter was then closed with interrupted atraumatic No 00 chromic catgut sutures A rubber drain was placed in the area and the wound was closed by the usual method

The specimen (fig 1, *D*) consisted of a long baseball bat shaped polyp, measuring 6 5 cm in length, 0 3 cm in diameter at the proximal end and gradually increasing in diameter up to 0 5 cm in diameter at the opposite distal end The surface was pinkish tan in color and covered by a thin film of blood in several places It was firm in consistency Microscopic examination confirmed the diagnosis of hemangioma (fig 1, *B*)

The patient made an uneventful recovery

DISCUSSION

Hematuria is frequently the initial and only symptom of a hemangioma in the urinary tract It is usually sudden in onset and its severity is no criterion of the size of the lesion In this case, there was a large tumor but only a minimal

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OBSTRUCTION OF THE LOWER THIRD OF THE URETER BY ANOMALOUS BLOOD VESSELS

LAURENCE F. GREENE, JAMES T. PRIESTLEY, HOWARD B. SIMON AND RICHARD H. HEMPSTEAD

From the Section of Urology and the Division of Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Obstructions of the ureter at or near the ureteropelvic junction by accessory or anomalous blood vessels represent a well-recognized entity. Whether the blood vessels are primary or secondary factors in the production of obstruction is polemic and need not concern us in this presentation. Cases of obstruction below the region of the ureteropelvic junction by patent blood vessels are unusual. Hyams[1] reported a case of obstruction in the lower third of the ureter by a blood vessel and mentioned briefly 4 similar cases.[2] In addition, there have been several reports of secondary vascular obstruction of the lower third of the ureter.[3-5] In each of these cases the primary cause of ureteral obstruction was situated at the ureterovesical junction. As a result of obstruction at this site the ureter became dilated and was compressed against a blood vessel; the blood vessel thereby became a secondary obstructive factor.

Hyams[1] studied and described the blood vessels of the lower part of the abdomen and the pelvis in cadavers. In 4 of these dissections vessels lying in close apposition to the lower third of the ureter were demonstrated; in all cases these vessels were tributaries of the anterior trunk of the hypogastric artery, principally the inferior vesical and umbilical vessels (before their obliteration).

We wish to report 2 cases of primary obstruction in the lower third of the ureter by patent blood vessels. In each case surgical exploration disclosed aberrant vessels as the sole cause for the obstruction; no other cause was found at or below the site of obstruction.

REPORT OF CASES

Case 1.—A 24-year-old man was first seen at the Mayo Clinic in July 1950, complaining of attacks of pain and discomfort in the left costovertebral angle that had occurred during the past 8 years. Three years prior to admission, while riding on a tractor, the patient noted the sudden onset of pain in the left costovertebral angle, which extended anteriorly and persisted for about 1 week. Four days prior to admission he "hurt" his back while lifting heavy bales of hay. On the following day he experienced pain in the left side of his abdomen, left flank and left costovertebral angle, accompanied by vomiting and fever.

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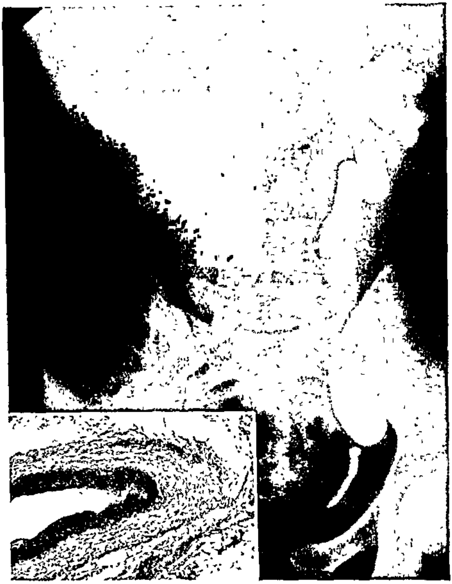

FIG. 1 (case 1). Left retrograde pyelo-ureterogram. *Inset.* Portion of wall of artery that was causing obstruction to ureter. Slight thickening of intima is present (hematoxylin and eosin; ×30).

Physical examination revealed moderate tenderness in the left costovertebral angle and left lower quadrant of the abdomen. The temperature was normal. The results of laboratory examinations were essentially normal except for microscopic erythrocyturia, grade 2 (30 cells per high power field).

An excretory urogram revealed delayed visualization of the left kidney and striking dilatation of the few calyces that could be seen; the right kidney was normal. A left retrograde pyelo-ureterogram (fig. 1) demonstrated dilatation of the pelvis and calyces. The ureter was grossly dilated and tortuous except for the lowermost several centimeters, which appeared normal. Cystoscopic examination gave negative results; the ureteral orifices appeared normal and passage of a catheter up the left ureter was unimpeded.

The patient improved symptomatically and was sent home, to return for further evaluation several months thence. He returned in August 1950, because of severe pain in the left upper quadrant of the abdomen, nausea and vomiting. The results of urologic examinations were similar to those noted at the time of previous examination.

A congenital anomaly of the left ureter was postulated, and surgical exploration advised and carried out. The left ureter was exposed through a left inguinal incision. Pronounced ureterectasis which extended well below the brim of the

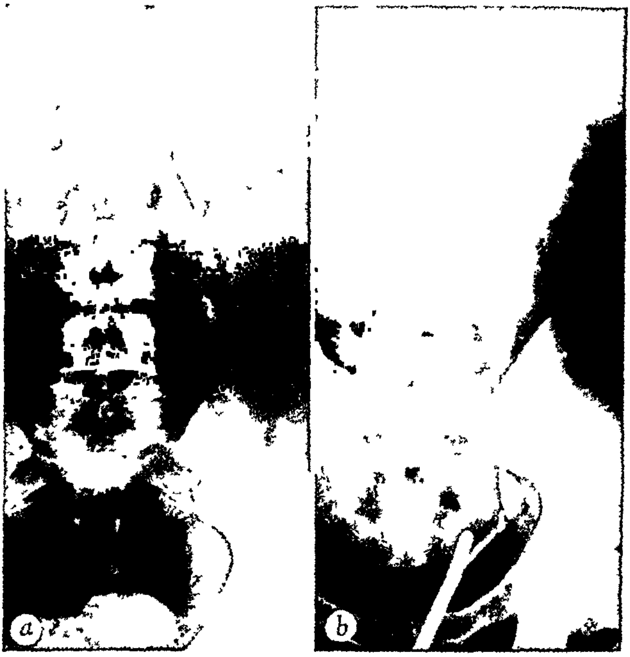

FIG. 2 (case 1) *a.* Excretory urogram and, *b*, left retrograde pyelo-ureterogram 7 months after operation.

pelvis was noted with a normal-sized ureteral segment below this point. The cause of the obstruction was several anomalous blood vessels which extended from the lateral side of the bony pelvis to the bladder and appeared to be anomalous inferior vesical vessels. The vessels were ligated and a section removed for pathologic study. The ureter was then opened through a small incision and its dilated portion proximal to the obstruction and the lumen of the ureter distally were explored from within. Intrinsic obstruction was not found and the ureteral incision was closed. The pathologic report of the excised vessels was "patent blood vessels" (fig. 1, *inset*).

The postoperative course was uneventful, and the patient was dismissed from the hospital on the eleventh postoperative day. Seven months later he returned at our request. His health was excellent and he had no symptoms. The excretory urogram and left retrograde pyelogram (fig. 2*a* and *b*) made at this time disclosed considerable improvement in the appearance and function of the left kidney. The urine was clear microscopically.

The patient was last seen in March 1952, at our request. His health had remained excellent and the results of urologic investigations were similar to those noted at the time of the last examination.

Case 2.—A 47-year-old man was first seen at the Mayo Clinic in June 1951, complaining of gross hematuria. Nine months before admission he noted "dull heaviness" in his left flank, and six months before admission he experienced initial hematuria during a period of twenty-four hours. He consulted a physician in his home community and an excretory urogram revealed left hydronephrosis with ureterectasis involving the upper two thirds of the ureter. Cystoscopic examination was carried out and a 3F ureteral catheter was passed to the left

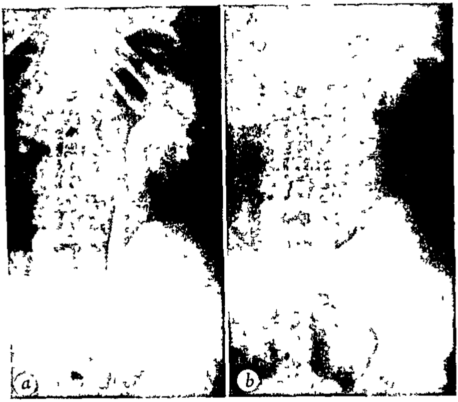

FIG. 3 (case 2). *a.* Left retrograde pyelo-ureterogram. *b.* Excretory urogram. (Courtesy of Dr. Angel F. Golderos, Havana, Cuba.)

kidney; an obstruction in the lower third of the ureter was noted in attempts to pass larger catheters. The ureter was subsequently dilated on several occasions to the diameter of a 8F catheter; febrile reactions followed such instrumentation. Otherwise, his symptoms had remained fairly mild.

At the time of admission to the Mayo Clinic the patient was afebrile and the results of physical examination were essentially negative. Urinalysis disclosed pyuria, grade 3, with both Proteus vulgaris and Pseudomonas aeruginosa found on culture. The results of other laboratory studies were normal or negative.

An excretory urogram demonstrated left pyelo-ureterectasis with the ureterectasis involving all but the lowermost several centimeters of the ureter, which appeared normal. The right kidney was normal. Cystoscopic examination revealed diffuse acute cystitis and a gaping, inflamed left ureteral orifice. A 5F catheter was passed to the left kidney, encountering obstruction in the lower portion of the left ureter, which was passed with some difficulty. There was rapid flow of urine through the catheter and thick inspissated pus was aspirated. Pseudomonas aeruginosa and Proteus vulgaris were cultured from this urine. A left pyelogram corroborated the findings noted by excretory urography (fig. 3*a*).

Surgical exploration of the lower part of the ureter was advised and performed in June 1951; a congenital anomaly of the ureter was considered the probable diagnosis. The left ureter was exposed through a low inguinal incision and was found to be dilated to a diameter of 2 cm. down to a point 3 or 4 cm. distal to the brim of the pelvis. At this point the ureter was compressed by anomalous vessels which were severed; below this point it appeared normal. The ureter was opened and explored from within, but an intrinsic obstructive lesion could not be found. A 10F catheter was passed into the bladder from the dilated portion of the ureter without difficulty. The ureter was closed around a No. 12 T tube, the long limb of which was passed through the previous site of obstruction; one suture was used for the closure.

The T tube was removed on the ninth postoperative day, and the wound healed rapidly. On the nineteenth postoperative day the patient was dismissed from our care. One year later his physician, Dr. Angel F. Golderos of Havana, Cuba, informed us by letter that the patient had experienced no further urologic difficulty, and the characteristics of an excretory urogram (fig. 3*b*) made at that time were within normal limits.

COMMENT

The term "hydro-ureter" is employed to describe an ill-defined group of cases in which ureterectasis is the dominant feature and in which the ureterovesical valve is competent. Megalo-ureter implies ureterectasis with incompetency of the ureterovesical valve. The etiologic agent in both conditions is unknown in many cases and of varied nature in others. It is our belief that the 2 cases described herein, in conjunction with the case described by Hyams,[1] establish the fact that hydro-ureter can result from obstruction due to anomalous blood vessels. These observations serve to separate a small group of cases of hydro-ureter of definite etiologic origin from the larger group in which the cause is indefinite or unknown.

In our opinion this anomaly represents a distinct pathologic entity, and one worthy of consideration in differential diagnosis. In each case, as seen roentgenographically, the obstruction was situated in the lower third of the ureter at a point midway between the bladder and the brim of the pelvis. The ureter was grossly dilated above this site and the dilatation was bulbous at the site of obstruction. The remaining lowermost portion of ureter was normal in each case. Cystoscopic examination and exploration of the ureter, both from within and without, did not disclose any other cause for obstruction. It may be fortuitous that involvement of the left ureter of an adult male was present in each case.

A correct diagnosis may be suggested by the urographic signs already described and corroborated by surgical exploration. The symptoms and other urologic findings in this condition are not distinctive.

SUMMARY

Two cases of hydronephrosis and hydro-ureter secondary to obstruction from anomalous vessels are described. In each case urographic study disclosed obstruction in the middle of the lower third of the ureter with ureterectasis above and a normal condition of the ureter below the site of obstruction. Excision of the offending blood vessels resulted in prompt disappearance of symptoms and in striking retrogression of the hydronephrosis and hydro-ureter. A definitive etiologic basis for a small group of cases of hydro-ureter is presented.

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NEW CONCEPT OF VESICAL INNERVATION AND ITS CLINICAL APPLICATION

LOWRAIN E McCREA and DONALD L KIMMEL

From Departments of Urology and Anatomy, Temple University School of Medicine and Hospital, Philadelphia, Pa

Many theories have been advanced by investigators as to the cause of vesical dysfunction following abdominoperineal proctosigmoidectomy or total hysterectomy with extended pelvic dissection It is our confirmed belief that vesical dysfunction following such a surgical procedure is of neurologic origin

It was originally considered that the behavior of the bladder following surgery suggested an imbalance due to a predominance of sympathetic innervation after the parasympathetic innervation had been subjected to trauma or excision It was also considered that regeneration of the parasympathetic innervation permitted a return to normal function Many of these statements have now been shown to be incorrect Regeneration of the nerve tissue is impossible, due not only to the extended excision of the nerve plexus, but also to massive scar formation in the tissues following surgery

It was to prove the cause and to prevent, if possible, the occurrence of vesical dysfunction that basic research on the innervation of the bladder was undertaken This study has consisted of the examination of serial sections of human fetuses ranging in size from 7 5 to 106 mm crown rump length This procedure or study has demonstrated that an accessory nerve supply to the bladder exists The nerve fibres are given off from the second, third and fourth sacral roots, traverse the deep layers of the endopelvic fascia by a perivascular route along the blood vessels within the lateral walls of the bony pelvis These nerves enter the bladder at the level of the insertion of the ureters (fig 1) They completely circumvent the usually acknowledged nervous pathways to the bladder through the pelvic plexus It has also been demonstrated that the newly described nerves are distributed in a pattern so as to completely overlap the distribution of the fibres which reach the bladder by way of the acknowledged pathway through the pelvic plexus (fig 2) It has been demonstrated that some of the fibres join the anterior part of the pelvic plexus, interrelating the two nerve routes to the bladder Nerves occupying a similar position have been indicated by Curtis, Anson, Ashley and Jones Pernkoff clearly demonstrates these nerves in their course to the bladder His illustrations, since based on gross dissections only, fail to show a representative number of these nerves lateral to the pudendal venus plexus

The usually acknowledge innervation of the bladder, according to Learmouth, arises from three sources These sources are the somatic, sympathetic and parasympathetic

The somatic innervation is supplied through the pudendal nerve, usually derived

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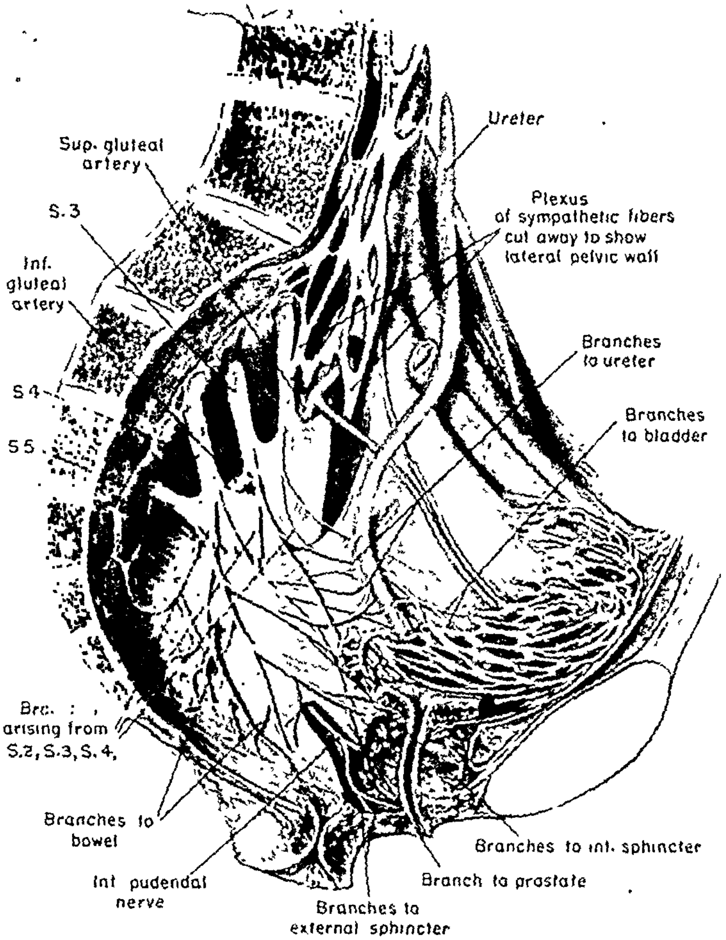
Ureter
Sup. gluteal artery
S.3
Inf. gluteal artery
S4
S5
Plexus of sympathetic fibers cut away to show lateral pelvic wall
Branches to ureter
Branches to bladder
Brc. [illegible] arising from S.2, S.3, S.4,
Branches to bowel
Int pudendal nerve
Branches to external sphincter
Branch to prostate
Branches to int. sphincter

FIG. 1. Dissection showing parasympathetic nerves to bladder.

from the second, third and fourth sacral roots. The distribution of this nerve is to the external sphincter, the striated muscle around the urethra. It is through this nerve that the only volutional impulses of urination are carried.

The sympathetic fibres which innervate the bladder are given off the thoracolumbar outflow from the first and second lumbar segments and possibly the twelfth thoracic segment. The sympathetic fibres to the bladder and other pelvic viscera are finally concentrated in a strand called the presacral nerve. At the promontory of the sacrum, the presacral nerve divides into the two hypogastric nerves which join the posterior superior angles of the corresponding ganglia or pelvic plexuses. From here, fibres pass onward to innervate the trigone, including the muscles of Bell, and the muscles of the crest of the urethra.

The parasympathetic fibres arise from the second, third and fourth sacral segments of the spinal cord and run through the pelvic plexuses which lie on the lateral surfaces of the rectum, to the bladder musculature.

In the surgical procedure of abdominoperineal proctosigmoidectomy, or in hysterectomy there is a disruption of the nerve fibres passing through the pelvic

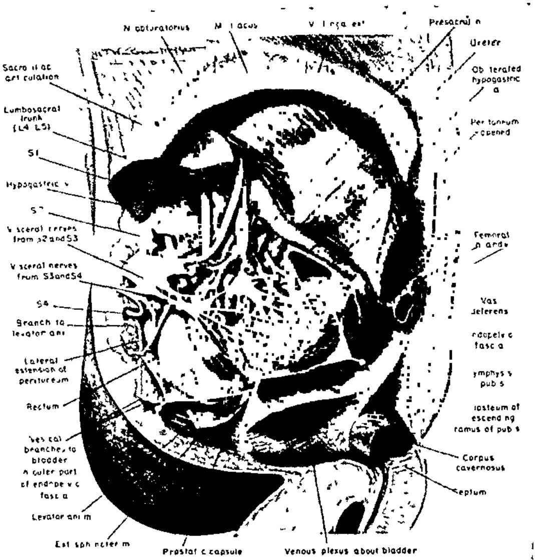
N. obturatorius
M. iliacus
V. iliaca ext.
Presacral n.
Ureter
Obliterated hypogastric a.
Peritoneum opened
Sacro iliac articulation
Lumbosacral trunk (L4 L5)
S1
Hypogastric v.
S2
Visceral nerves from S2 and S3
Visceral nerves from S3 and S4
S4
Branch to levator ani
Lateral extension of peritoneum
Rectum
Vesical branches to bladder in outer part of endopelvic fascia
Levator ani m.
Ext. sphincter m.
Prostatic capsule
Venous plexus about bladder
Femoral
Vas deferens
Endopelvic fascia
Symphysis pubis
Periosteum of descending ramus of pubis
Corpus cavernosus
Septum

FIG. 2. Parasympathetic nerves seen to enter inferior hypogastric or pelvic plexus together with sympathetic fibres. Pudendal nerve is in a normal position and is not in direct communication with other nerves that control urination. It is through pudendal that only volutional impulses or urination are carried.

plexus. It is believed that the newly described accessory fibres completely take over the function of the innervation of the bladder when the posterior portion of pelvic plexus is disrupted. It is further believed that vesical atonia or dysfunction is usually temporary, but may be permanent. It is not believed that vesical dysfunction is due to obstructive uropathy as some investigators would lead us to believe. If this were true, it would be difficult to explain how urinary dysfunction following proctosigmoidectomy or hysterectomy occurs in women or in men below the "prostatic age" without visible or palpable evidence of benign prostate hyperplastic change. Granted, a certain percentage of individuals, on whom bowel resection is done, are within the prostatic age and may develop urinary retention. There is no disagreement as to the cause of treatment of such retention. However, it is not considered necessary to do transurethral resection in every instance of temporary vesical atonia following such surgery.

Permanent vesical atonia would result when the pelvic plexus, which is considered to be the primary nerve pathway to the bladder is excised, and there was extensive trauma to the accessory nerves coursing to the bladder in the lateral endopelvic fascia. When once established it is doubtful whether transurethral resection is the answer. A bladder in such a state is dilated or easily dilatable and is without tone as interpreted by the cystometer.

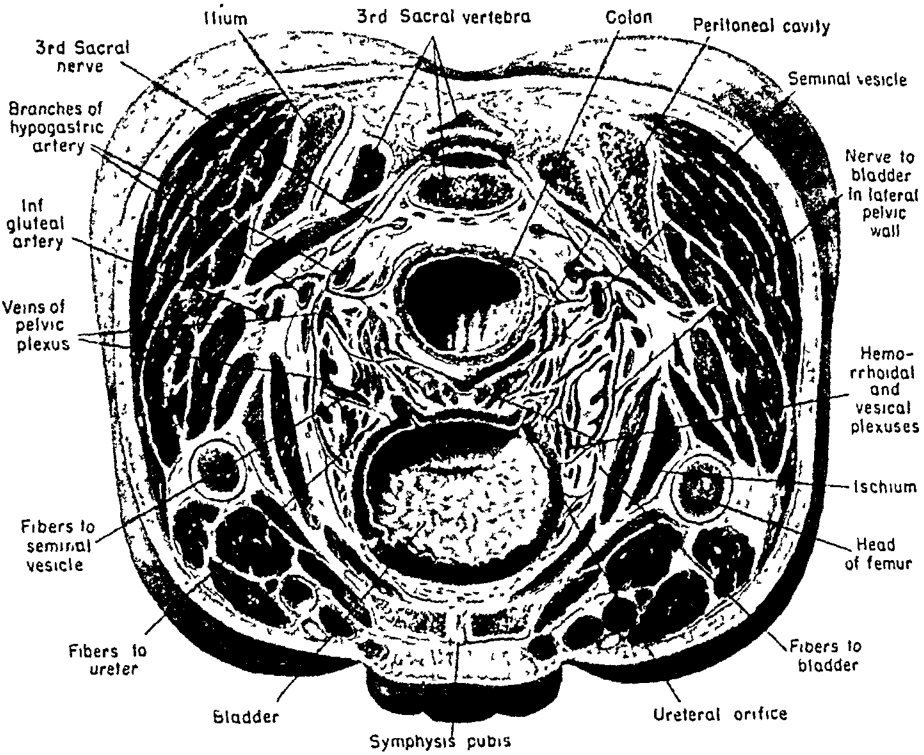

FIG 3. Cross section through pelvis of an adult male showing position of nerves to bladder as they course through endopelvic fascia.

Note particularly relationship of nerves to blood vessels and their later position in endopelvic fascia.

It is established that nerves reach the bladder by two separate and distinct routes. These routes are 1) the established pathways through the inferior hypogastric or pelvic plexuses and 2) the newly described pathways, coursing to the bladder by a perivascular route. The nerves of the newly described pathways are given off from the second, third and fourth sacral roots and course to the bladder along the blood vessels in the endopelvic fascia within the lateral walls of the bony pelvis (fig. 3). Many of these nerves run to their termination on the ureter and bladder independently of the pelvic plexus. Others join the pelvic plexus anteriorly to the rectum in the lateral wall of the rectovesical fossa. It is believed that the presence of these nerves in their lateral position explains normal bladder function following removal of the rectum or the uterus. It is believed that trauma to the nerve supply of the bladder rather than obstructive uropathy, is the cause of vesical dysfunction following extended pelvic surgery such as abdominoperineal proctosigmoidectomy or total hysterectomy with extended dissection.

CONCLUSION

An accessory innervation to the bladder has been demonstrated. As stated it is believed that these nerves do and are capable of maintaining normal vesical function following many types of pelvic surgery.

1930 Chestnut St., Philadelphia, Pa.

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ENURESIS

S. HARRIS JOHNSON, III AND MATTHEW MARSHALL, JR.

From Children's Hospital, University of Pittsburgh Medical Center, Pittsburgh, Pa.

Enuresis is the unintentional and unconscious voiding of urine; usually, in a full steady stream, occurring predominantly during sleep. It has been recognized as an abnormality in childhood, at least as early as the year 1550 B.C. when it was mentioned in the Papyrus Ebers. Persistence of enuresis after the age of ten years in boys and after the onset of menstruation in girls is unusual and usually indicates an organic lesion or a marked psychogenic problem. Correction of this symptom state before this age is important, because the prognosis is in inverse ratio to the duration, and persistent enuresis retards normal development of the child into a stable adult and discourages a normal healthy home life and parent relationship.

ETIOLOGY

Enuresis falls into two categories; true enuresis, which is functional or psychogenic in origin, and organic enuresis. True enuresis is considered a personality disorder due to a single or a combination of psychological conditions in the child. These are chiefly a subconscious resentment toward the parents, a subconscious wish to remain in, or return to, the protected irresponsible stage of infancy, or a lack of maturity with particular reference to bladder control. Organic enuresis is due to uropathological changes. These changes are chiefly in the lower urinary tract. Bedwetting or frequency caused by infection is not true organic enuresis, but often it is treated as a functional state, its potential gravity being unrecognized. Neuromuscular dysfunction of the bladder, urethral diverticulum, or ectopic ureteral orifices do not fall within the category of enuresis but rather in that of incontinence or pseudo-incontinence. Although spina bifida occulta has been advanced as a cause of enuresis, it is associated with neuromuscular dysfunction of the bladder in not over 5 per cent of cases, and cannot be considered a major etiological factor.

DIAGNOSIS

Fundamentally, it is essential from the diagnostic and treatment standpoint to differentiate the true or functional enuretic from the enuretic due to organic disease of infectious, obstructive, or neurogenic variety. Urological investigation is necessary for this differentiation. An attempt has been made to describe a pathognomonic urethroscopic picture of enuresis, but it has not been generally accepted nor has it been found in our experience. Although cysto-urethrography has been found by us to be of definite value, cysto-urethroscopy and pyelography remain the diagnostic method of primary importance. In our experience, the technical difficulties in the application and interpretation of cystometry when used in infants and children preclude its extensive use.

Condensed report of paper read at annual meeting, Northeastern Section, American Urological Association, at sea, aboard S.S. Ocean Monarch, October 9, 1952.

TREATMENT

There is no specific treatment for enuresis but inumerable drugs and methods have been advocated. Much can be accomplished by prophylactic care directed towards its prevention. It is most important that the parents realize that the basic cause of functional enuresis is theirs and that a cure depends upon their minimizing the problem in an unemotional way. The expert assistance of a qualified child psychiatrist or psychologist, particularly in the management of an emotional, neurotic child, is ideal but unfortunately their services are too restricted in time and numbers to be of great value to the large numbers of bedwetters. Therefore, the burden of tactful, wise and sympathetic guidance falls upon the shoulders of the family pediatrician or physician who, if he understands the problem, is best suited for this task. Nocturnal behavior training is of definite value, but the child should be thoroughly awakened, otherwise the habit may be exaggerated.

The limitation of fluids and a dry supper may seem logical but have no scientific basis, for a normal well compensated bladder should accomodate itself to any reasonable fluid intake. Drugs have been used throughout the ages in order to induce children to remain dry. Of recent years tincture of belladonna, ephedrine sulphate, amphetamine sulphate, methyl testosterone, chorionic gonadotropin and salt in addition to physiotherapeutic means have been used, the results varying with their advocates' enthusiasm.

Recently, instrumental means of curing enuresis, the mechanics of which are based on the Pavlov theory of conditioned reflexes, have come to the forefront. Of these, the most successful basic device to cure functional enuresis was devised in 1938, by Mowrer and Mowrer. In 1946, Sieger incorporated both a bell and a light as a conditioning stimulus, and made the apparatus more easily handled and more sensitive in response. This apparatus is commercially available on a rental basis to patients, and is known as the Enurtone. The Enurtone Company conducted a questionnaire survey of 475 patients who had used their apparatus. They claim that a reply from 174 cases of enuretic children with a mean age of 8.4 years showed that there were 76 per cent who had achieved a cure, based on thirty consecutive dry nights. A random sample survey of 57 who did not reply to the mail inquiry indicated a success rate of 72 per cent using the same criteria. We have recommended its use for patients in whom organic enuresis had been eliminated, with satisfactory results. Our objection to it is, the commercial basis on which it is available; its being advertised as a cure for enuresis and used without medical advice or investigation; and, from the standpoint of parents of patients, its cost.

Although only 5 to 10 per cent of all enuretics fall into the organic category, strictly urologic treatment has a definite place in the treatment of enuresis, for more than one-half of those failing to respond to intensive medical or psychological treatment are found to have organic disease.

REPORT OF CASES

We have reviewed 314 cases referred for the study of enuresis to Children's Hospital in the past 6 years. The majority of these had had previous medical

TABLE 1

Functional		146—46 5%
Organic		
Neuromuscular deficiency	14	
Cystitis (positive culture)	30	
Epispadias	1	
Diabetes mellitus	1	
True organic	122	
Total		168—53.5%
Total cases		314

and/or psychiatric care of routine type. Of these cases, 303 were from three to fifteen years of age; 130 were girls, and the large majority were of the white race. Nocturnal enuresis alone was present in 269 cases, or 86 per cent, and both diurnal and nocturnal enuresis in 44 cases, or 14 per cent. There was one case of diurnal enuresis. Uropathology was found in 168, or 54 per cent of the enuretics. This agrees well with the generally accepted statistical occurrence of organic enuresis among cases referred for study following failure of routine treatment (table 1).

Among the group having organic pathological changes, however, are some who cannot be considered true enuretics. These are 14 cases found to have neuromuscular dysfunction of the bladder; 1 with diabetes mellitus; 1 with epispadias; and 30 cases of cystitis with a positive urine culture; leaving 122 cases with true organic enuresis. Of the 168 cases exhibiting pathological changes, 66 cases had urinary tract symptoms in addition to enuresis, while only 24 of the 314 cases of functional enuresis had additional urinary tract symptoms. Upper urinary tract abnormality was found in 29 cases, or 9.0 per cent. Various types of treatment were carried out in the cases of both functional and organic enuresis (table 2). Specific antimicrobial therapy in the 30 cases of cystitis having positive urine cultures resulted in 19, or 63 per cent cures; in 2 showing improvement; in 5 failures; and 4 in which the result was undetermined.

Urethral dilatation was used as treatment in 12 cases of urethrotrigonitis, resulting in 6, or 50 per cent cures; 2 improved; 2 failures; and 2 of undetermined result. Seventeen functional enuretics underwent urethral dilatation and 9, or 53 per cent were cured. There were 4 cases each of failure and undetermined result.

Meatotomy for stricture of the urethral meatus was carried out 35 times. This procedure was rewarded with 18, or 51 per cent, cures; 2 improved; 8 failures; and 7 cases of undetermined result.

Posterior urethral congenital valves were excised transurethrally in 4 cases; 2, or 50 per cent, of which were cured; 1 improved; and 1 continued to have enuresis.

Five cases of enuresis were found to have a contracture of the bladder neck

TABLE 2

PROCEDURE	TYPE OF CASE	NO OF CASES	CURE	IMPROVED	FAILURE	UNDETERMINED
Antimicrobials	Cystitis (positive culture)	30	19–63%	2	5	4
Urethral dilatation	Urethrotrigonitis	12	6–50%	2	2	2
	Stricture	73	33–45%	12	16	12
	Functional enuresis	17	9–53%	—	4	4
Meatotomy	Stricture urethral meatus	35	18 51%	2	8	7
T U R	Posterior urethral congenital valves	4	2 50%	1	1	—
	Contracture bladder neck	5	5 100%	—	—	—
Fulguration	Verumontanum (hypertrophy inflammation)	25	12–48%	2	6	5
Circumcision	Prepuce, redundant, phimosis balanitis	20	6–30%	1	13	—
Banthine	Hypertonic bladder	6	2 33%	2	2	—
Chorionic gonadotropin	Functional enuresis, hypogenitalism	40	10–25%	11	17	2
Methyl testosterone	Functional enuresis, hypo*genitalism*	39	13 34%	13	11	2
Enurtone	Functional enuresis	12	11 92%	1	—	—
No treatment	Functional enuresis	70	—	—	—	—

requiring transurethral resection This *resulted in a cure in all 5 cases, or 100* per cent

Fulguration of the verumontanum was done in 25 cases, for hypertrophy, polyps, granulomas and inflammation A cure of the enuresis resulted in 12 or 38 per cent of the cases There were 2 improved, 6 failures, and 5 cases having undetermined results

Circumcision for phimosis, redundant prepuce and recurrent balanoposthitis was followed by cures in 6, or 30 per cent, of the cases There was 1 improved, *and 13 failures*

Banthine was used in 6 cases, with cure in 2, or 33 per cent, of the cases, improvement in 2 cases, and failure in 2 cases

Chorionic gonadotropin was used in the treatment of 40 cases This therapy *resulted in 10, or 25 per cent, cures* There were 11 cases showing improvement, and 17 failures, the result in 2 cases was undetermined

Methyl testosterone was *administered by mouth to 39 children with enuresis,* the majority of whom had underdeveloped genitalia In this group there were *13, or 34 per cent cures* Thirteen cases were improved, 11 cases resulted in failure, and in 2 cases the result was undetermined

The Seiger type apparatus has been used by 12 of our cases This stimulus conditioning therapy has resulted in 11, or 92 per cent cures, and in 1 improvement

Seventy cases of functional enuresis in this series did not receive any of the reported types of treatment

CONCLUSIONS

The mechanism of functional enuresis has not been determined as yet. There are considerable data which point toward the premise that it is due to failure of the conditioning of a bladder voiding reflex on a training or psychological basis. In a large group of enuretics who have not responded to routine medical or psychiatric treatment, over 50 per cent will be found to have organic changes in the urinary tract. This is ample justification for the continuation of complete urological investigation of children having refractory enuresis, particularly those having additional symptoms of urinary tract instability. Correction of these abnormalities may not cure enuresis. In fact, the general average of cures in organic enuresis is not significantly much greater than that obtained in functional enuresis with many empirical types of therapy. Therefore, many children found to have uropathological changes may, in truth, be functional enuretics. However, correction of urinary tract abnormalities is essential to prevent the occurrence later of irreparable damage. There is no specific treatment for enuresis. At this time, the best generally available treatment appears to be the Seiger type apparatus which produces a normally conditioned bladder reflex. In our opinion it should not be used without regard to existing uropathology which might result in late untoward results.

SUMMARY

The history of the concepts concerning, and treatment of, enuresis from antiquity to the present is reviewed.

Three hundred and fourteen cases of enuresis are reported in regard to uropathology found, and results of treatment.

901–903A Peoples East End Bldg., Pittsburgh 6, Pa.

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THE ROLE OF THE URINE IN VESICAL NEOPLASM.
1. EXPERIMENTAL CONFIRMATION OF THE UROGENOUS THEORY OF PATHOGENESIS

DONALD F. McDONALD AND ROLAND R. LUND

From the Division of Genito-Urinary Surgery of the University of Washington School of Medicine, Seattle, Wash.

The problems prompting this experiment were twofold. Do the urinary constituents play an important part in producing experimental bladder tumors? Secondly, will established experimental tumors regress when deprived of contact with urine? Both questions have been answered. The carcinogen reached the bladder in effective concentration only in the urine. Once established the tumors no longer required continued contact with carcinogen or urine.

METHODS

In ten young adult female mongrel dogs and twenty-nine adult male rabbits the dome half of the urinary bladder was surgically transformed into a pouch isolated from contact with the urine. The method varied slightly in the two species but in all cases care was taken to preserve the blood supply to the pouch (fig. 1). The choice of sex in the two species was determined by the greater ease of cystoscopy in female dogs and male rabbits. At the time of surgery the bladders were inspected to rule out pre-existing lesions.

The animals received the carcinogen, beta-naphthylamine orally. Capsules containing 600 mg. were given daily to the dogs. A 0.1 per cent solution of beta-naphthylamine hydrochloride was given ad libitum to the rabbits in place of drinking water. The daily voluntary intake averaged 350 mg. The hydrochloride of beta-naphthylamine was prepared freshly because it deteriorated. The animals were weighed weekly. The diet of the rabbits consisted of commercial pellets, fresh lettuce and carrots. The dogs received canned dog food and meal and fresh horse meat.

Cystoscopy was performed at monthly intervals with the 16F cystoscope. This was accomplished without the need for anesthesia in rabbits but dogs required general anesthesia. When well-established tumors were demonstrated, the dogs were explored surgically, the lesions photographed and biopsied, and the urinary stream diverted. Ureterovaginostomy and transplantation of the ureters to the pouch with drainage of the pouch by polyethylene cystostomy tube were more successful methods than ureterosigmoidostomy. Following deviation of the urinary stream no further carcinogen was administered. The method of Bratton and Marshall was used for the determination of urinary aromatic amine.

This work was supported in part by a Grant-in-aid from the National Cancer Institute of the U. S. Public Health Service, by Initiative 171 Research Funds provided by the State of Washington for research in the biological and medical sciences and by the John and Mary R. Markle Foundation.

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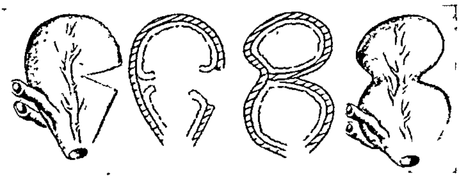

FIG. 1. Method of preparing bladder pouch in dogs. From left to right: incision in anterior wall of bladder, mobilization and incision of mucosa, suture of mucosa and muscularis separately, external appearance of completed pouch.

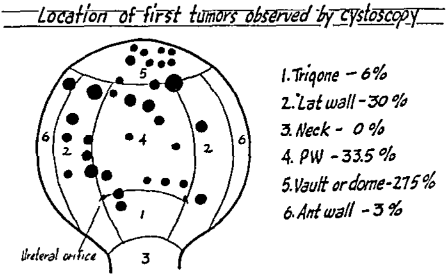

FIG. 2. Location of first tumors seen on cystoscopy in dogs treated with beta-naphthylamine.

RESULTS

1) Dogs. As early as two weeks after initiating treatment intermittent melena (four plus benzidine reaction) occurred in five animals. This was more prevalent with beta-naphthylamine than with the hydrochloride. Gastro-intestinal bleeding was never a serious problem. By two months all dogs showed microscopic hematuria which continued throughout the experiment.

The first cystoscopic lesion seen was hyperemia about the ureteral orifices after an average latent period of nine months. After an average additional interval of two months, telangiectases were noted in the bladder wall. Over some of these telangiectases small brown spots suggestive of epithelial thickening were noted. The thickened epithelium in some cases resembled cystic bullous lesions. The dark brown spots and the cystic lesions were observed to enlarge until recognizable as papillary tumors. These were delicate and bled easily when traumatized. Some of the tumors grew to large sessile infiltrating carcinomas. The locations for the first tumors were: posterior wall 33.5 per cent, lateral walls 30 per cent, dome 27.5 per cent, trigone 6 per cent, anterior wall 3 per cent (fig. 2). After the first tumor appeared others developed with remarkable rapidity. As many as eight new tumors appeared in one month. Four dogs eventually developed papillomatosis covering the entire interior surface of the urinary bladder. In one animal the neoplasm extended into the urethra. Table 1 summarizes the relationship of total dose to latent period and position of the first tumors seen. Tumors were absent from the pouches of all dogs except one in

TABLE 1. *Relationship between tumor induction time, total dose of carcinogen and number and location of first observed tumors*

DOG	β-NAPHTHYLAMINE TOTAL DOSE, GRAMS	INDUCTION PERIOD, MONTHS	NUMBER OF TUMORS	LOCATION OF TUMORS
54	136	8¼	3	1 posterior wall 1 right posterior wall 1 left posterior wall
37	124	11	1	Right lateral wall
39	124	11	1	Right lateral wall
41	139	11	2	Posterior wall
35	150	12⅔	6	3 dome 3 left posterior wall
34	234	13½	3	2 dome 1 right trigone
36	247	13½	2	2 left ureteral orifice
32	280	13¾	7	3 posterior wall 4 right posterior wall
45	590	16	3	1 right anterior wall 2 posterior wall
33	258	17	4	1 right lateral wall 3 dome

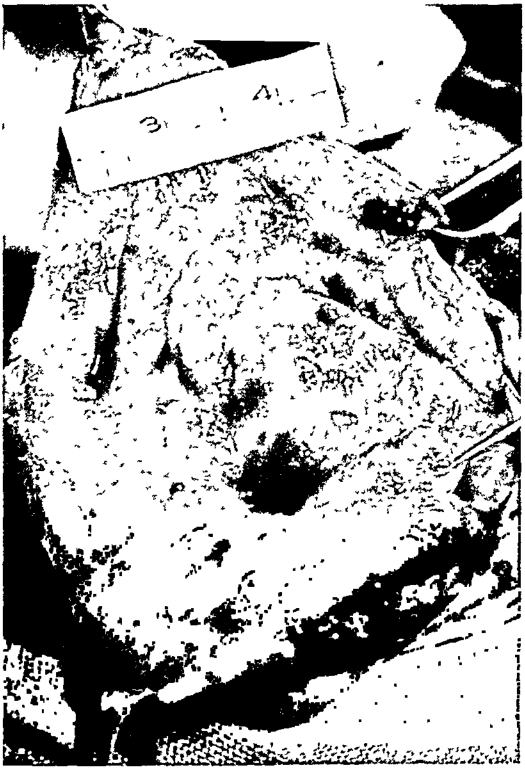

FIG. 3. Dog 34 bladder photograph looking down at vesical neck showing multiple small tumors.

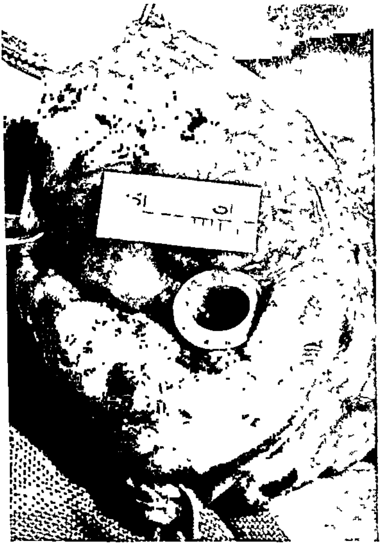

FIG. 4. Dog 34 pouch. Multiple tumors occurring in pouch due to communication (rubber tubing inserted in ostium for demonstration purposes) with bladder which permitted contact of urine with epithelium of pouch This was the only pouch which was found to contain tumors.

which there was a communication of the pouch with the bladder which permitted a free flow of urine into the pouch (figs. 3 and 4). In no case did tumors develop in bladder epithelium not in contact with the urine.

The excretion of aromatic amines in the urine of the treated dogs was found to vary from 1.25 to 4.5 mg. per ml. with an average of 3.3 mg. per ml. in 33 tests. Normal dogs excrete an average of 1.0 mg. per ml. of aromatic amine. Fluid aspirated from bladder pouches did not give the qualitative test for aromatic amines.

Histological grading of the tumors by the method of Col. J. E. Ash of the Army Institute of Pathology showed variation from grade one to three transitional cell carcinoma with squamous cell components in eight specimens (fig. 5). Most of the tumors were papillary and of grade two malignancy. Extensive invasion of the bladder wall was noted in six. No distant metastases were found. In one section a tumor embolus in a blood vessel was noted (fig. 6). Nearly all of the tumors showed adjacent submucosal leukocytic infiltration. Some showed frank necrosis and infection. Hyperemia was always present at the base of the tumor. The cell nests of von Brunn, which are submucosal groups of urinary epithelial cells, were observed to be hyperplastic in half of the specimens. In one dog these nests developed into cystitis cystica and cystitis glandularis. The cell nests had no constant relationship to the tumors.

TABLE 1. *Relationship between tumor induction time, total dose of carcinogen and number and location of first observed tumors*

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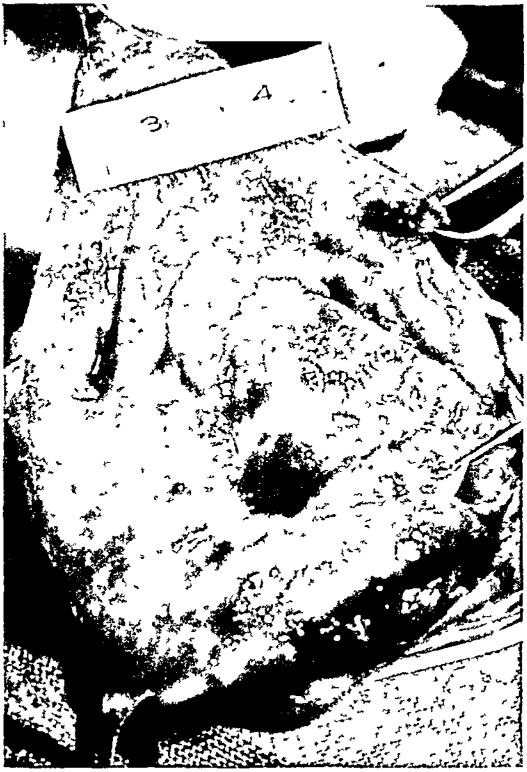

FIG. 3. Dog 34 bladder photograph looking down at vesical neck showing multiple small tumors.

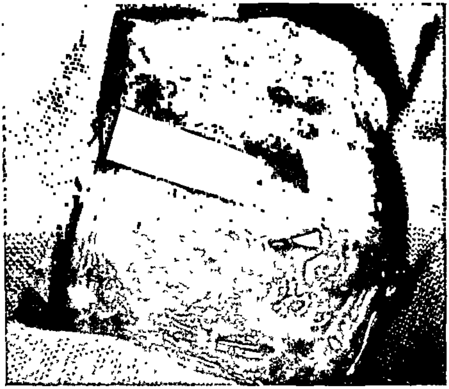

FIG. 7. Dog 36. Bladder at time of exploration and just prior to deviation of urine. Multiple small tumors are present.

The urine was successfully deviated from the tumors in five dogs. After one, two, three, four and one-half and five months of freedom from contact with the urine the neoplasms continued to grow (figs. 7, 8, 9 and 10). There was neither gross nor microscopic evidence of regression. No papillary tumors were found in the ureters or renal pelves. In two dogs hyperplasia and renal tubular adenoma formation were seen (fig. 11). In one section an early transitional cell carcinoma was seen in the renal medulla (fig. 12).

Toxic effects were produced by beta-naphthylamine. One dog died after six months of treatment, probably due to distemper. She received 200 mg. daily of the hydrochloride for a total dose of 36 gm. Death occurred one week after hematuria became marked. Necropsy showed hemosiderin deposits and vacuolization of the renal tubules. There were granular and red cell casts in the collecting tubules. Routine post-mortem examinations of other dogs treated for much longer periods showed extensive hemosiderosis of the kidney, liver and spleen. Slight renal tubular degeneration and fatty infiltration of the liver were common. Chronic purulent vaginitis and pyelonephritis occurred in all dogs subject to ureterovaginostomy. Areas of hyperemia in the intestinal mucosa were seen in two animals but no other lesions of the gastro-intestinal tract were observed. All dogs gradually lost weight during the two year study. This, however, was not of such degree that it interfered with the general health and activity of the animal with one exception. A Collie required several two to three week interruptions of treatment to restore its appetite and activity.

2) Rabbits. No neoplastic lesions were noted in the bladder or pouch of rabbits after two years of treatment. Other proliferative lesions occurred as shown in table 2. Proliferation of von Brunn's cell nests was noted in the area of the healing mucosa within one month after the first operation. Two other rabbits showed

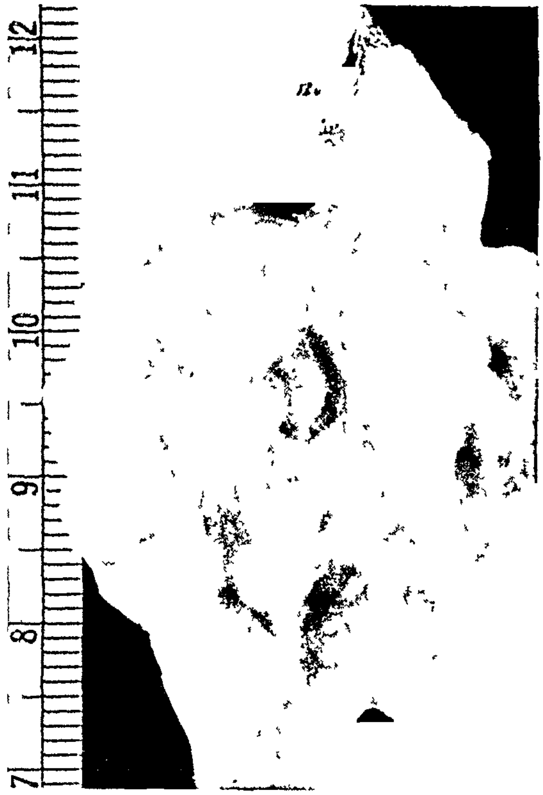

FIG. 8. Dog 36. Bladder three months after deviation of the urinary stream and discontinuance of beta-naphthylamine. Multiple large tumors are present.

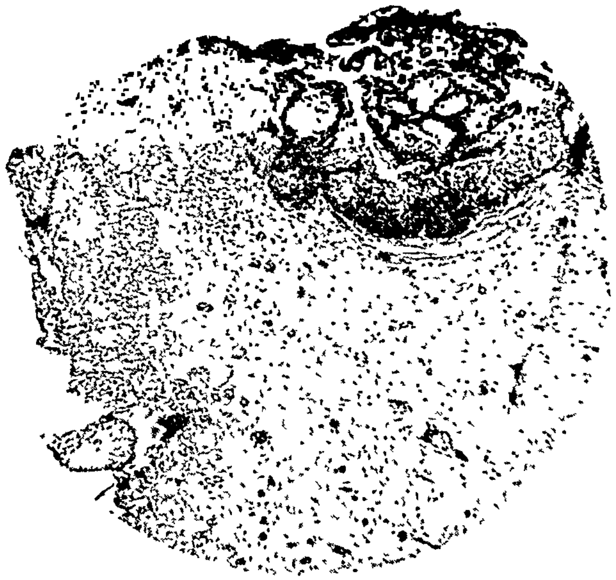

FIG. 9. Dog 41. Biopsy of tumor taken at time of deviation of urine. Note lack of invasion.

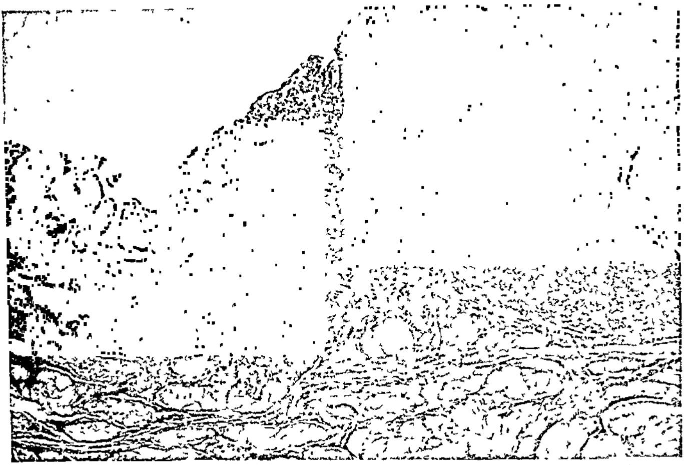

FIG. 10 Dog 41. Highly invasive carcinoma of bladder 1 month after deviation of the urine

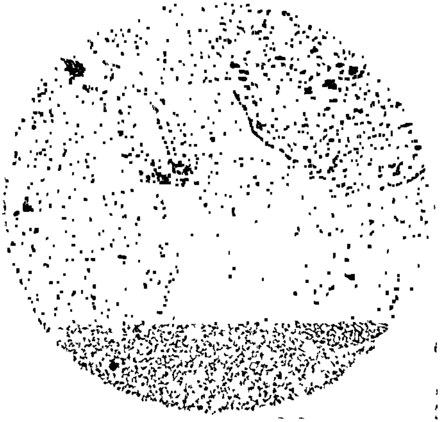

FIG. 11. Dog 34. Tubular adenomas and transitional cell carcinoma of kidney after 16 months' exposure to beta-naphthylamine.

these changes in both the bladder and pouch after three months and nine months. Twelve rabbits showed cystitis cystica and cystitis glandularis after an average induction period of 21 months with a range of twelve to twenty-four months. Grossly, the lesions varied from minute solitary structures to a thickened mucosa

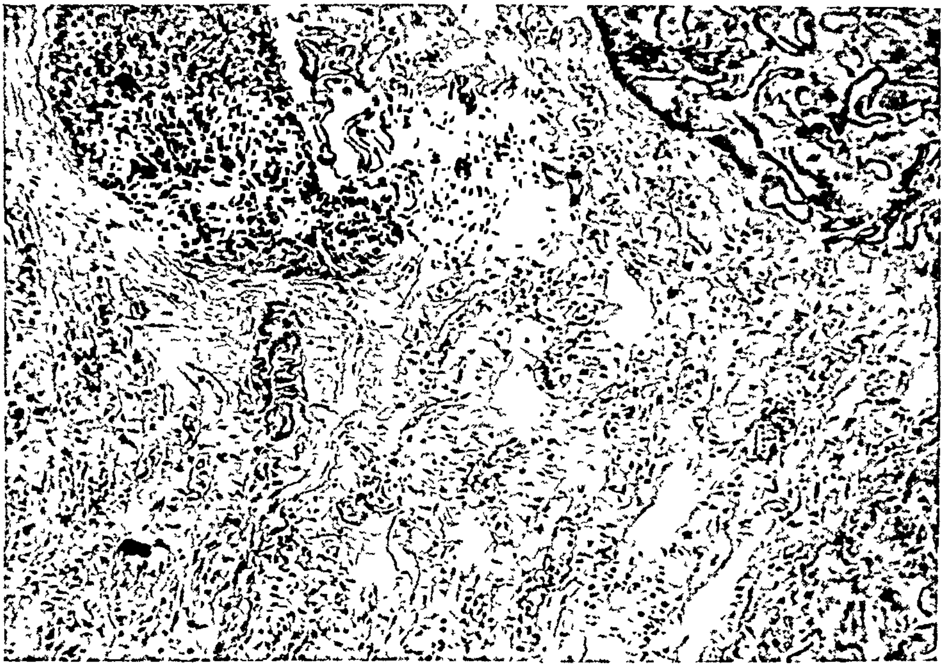

FIG. 12. Dog 34. Early transitional cell carcinoma of renal pyramid

TABLE 2. *Proliferative lesions in rabbits treated with beta-naphthylamine*

LESION	NUMBER OF ANIMALS	TREATMENT TIME
Von Brunn's cell nests	3	4 months
Cystitis cystica and cystitis glandularis	12	21 months
Bladder polyps	2	20 months
Squamous metaplasia of bladder	3	23 months
Epithelial hyperplasia of renal pelvis	7	24 months
Leucemia	1	9 months
Proliferation of bile ducts	2	24 months

resembling tapioca on surface view and resembling sponge rubber on cut section. In five of these animals the cystitis was found in both the bladder and the pouch. In six the cystitis was found in the bladder only; and in one, the pouch only. Those pouches having the lesions were infected. Microscopically the lesions were typical. Moderate round cell infiltration was observed in the region of the cysts. Two rabbits developed polyps consisting largely of connective tissue with some infiltration by plasma cells and lymphocytes. There was no change in the epithelium which was focally absent. Squamous metaplasia of the bladder was found in three rabbits and hyperplasia of the renal pelvis epithelium was found in seven rabbits at twenty-four months. Lesions of a neoplastic nature occurred in three rabbits. One of these developed leucemia after nine months. The lungs, liver, kidneys and most other organs of the body were infiltrated with the leucemia cells. Two other animals, sacrificed after two years were found to have multiple heptic nodules which microscopically were adenomatous proliferations of bile ducts with well differentiated structure. In one rabbit ectopic bone formed in the submucosa of the pouch.

Cyanosis appeared in rabbits given 0.2 per cent beta-naphthylamine hydrochloride solutions ad libitum in lieu of drinking water after three weeks exposure. Cyanosis was marked in seven rabbits and present in five others. Reduction of the concentration to 0.1 per cent prevented cyanosis. Hematuria did not occur in rabbits. Post-mortem examination showed a urinary tract infection with pyelonephritis in six animals and chronic inflammatory changes in the bladder of most animals. Renal tubular degeneration and hemosiderosis in the liver, spleen and kidney were characteristic findings.

Rabbits who excreted primary amines in acetylated form were found to have no free aromatic amines in the urine as opposed to the dogs who excreted it all in free form. After hydrolysis there was range of 1.15 to 5.5 mg. per ml. with an average of 3.0 mg. per ml. in 19 determinations on rabbit urine.

DISCUSSION

The experiments clearly show that urinary constituents have an etiologic role in the production of beta-naphthylamine bladder tumors in dogs. In no case did carcinoma develop in epithelium not in contact with urine. In every dog carcinoma developed in the bladder epithelium in contact with the urine. If a blood-borne carcinogen were responsible for tumor growth, then neoplastic change should have developed in the bladder epithelium in the pouch which had an intact blood supply. Neoplastic change occurring in the pouch of the animal whose pouch communicated with the bladder and hence contained urine demonstrated that the pouch epithelium was just as susceptible as the bladder epithelium when properly stimulated. The active urinary carcinogen was not identified in this study but the work of Mellors and Hlinka indicates that it is present in both blood and urine. Bonser, Clayson and Jull showed that 2-amino-1-naphthol, the probable active metabolite of beta-naphthylamine, is 200 times more concentrated in the urine than in the blood of dogs. These observations in addition to the direct evidence of the present experiment substantiate the urogenous theory of vesical carcinogenesis. Even though the active carcinogen is present in both the blood and the urine it is effective only in the high concentration found in the urine.

The fact that hyperemia and telangiectasis were the first lesions noted on cystoscopy does not necessarily indicate a hematogenous route as Ferguson and Gay advocate. Rather it may indicate that the urine-borne carcinogen is acting as an irritant with resulting hyperemia, and/or that the growth stimulating properties of the carcinogen have progressed to the point of preparing a blood supply for the newly forming epithelial tumor.

The primary location of the tumors does not correspond with the findings of Hueper, Wiley and Wolfe who found induced tumors to be mostly on the dependent portions of the bladder. In this study very few tumors appeared on the anterior wall. It is certainly true that all surfaces of the urinary bladder are constantly wet with urine and dependency can play only a minor role.

In the rabbits the cystitis cystica and glandularis, the polyps and squamous metaplasia are interpreted to be nonspecific lesions due to trauma and infection.

Hueper's observation (Hueper, Briggs and Wolfe) that in experimental bladder tumors distant metastases are rare but local invasion is common is confirmed. This is also true in humans (Stirling and Ash; Waller and Hamer). All of the dogs developed tumors despite a mixed genetic background although it is true that there was a variation in the quantity of carcinogen apparently required and the time of induction. The intensity of the stimulus in our experiment, 600 mg. daily, as compared with 450 mg. given in Hueper's series, reduced the average induction time from twenty months to twelve and three-fourths months.

Deviation of the urine and cessation of the carcinogenic stimulus did not inhibit the growth of the tumors. This is the usual observation in cancer. Once the process is firmly established it continues without further need of exogenous stimulation. Regression of bladder tumors in humans has been reported following deviation of the urine (Davis; Abeshouse and Scherlis) but often no beneficial influence derives from this procedure. We were not able to confirm by this experiment that deviation of the urine from established tumors results in their regression.

The renal adenoma and early transitional cell carcinoma of the duct of Bellini are interpreted as neoplastic responses to the beta-naphthylamine. To our knowledge such lesions have not been previously reported. The leucemia in one rabbit may have been coincidental although spontaneous leucemia in rabbits is rare. The hepatic duct proliferations in two rabbits may have also been coincidental.

CONCLUSIONS

Bladder tumors can be easily induced in dogs by beta-naphthylamine.

Rabbits are resistant to induction of beta-naphthylamine tumors in the dose and time selected, but hyperplasia and metaplasia may result.

Epithelial contact with the urine is essential to the production of experimental bladder tumors in dogs. This confirms the urogenous theory of vesical carcinogenesis.

Deviation of the urine from established experimental bladder tumors does not inhibit their growth.

Renal adenoma and early transitional cell carcinoma of the collecting duct epithelium may be induced by beta-naphthylamine.

B-511 Health Sciences Bldg., University of Washington, Seattle, Wash.

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A RESTUDY OF THE FIRST FOURTEEN HUNDRED TUMORS IN THE BLADDER TUMOR REGISTRY, ARMED FORCES INSTITUTE OF PATHOLOGY

A L DEAN, F K MOSTOFI,* R V THOMSON AND M L CLARK

From the Armed Forces Institute of Pathology Bladder Tumor Registry of the American Registry of Pathology, Washington, D C

This study was undertaken at the request of the Executive Committee of the American Urological Association in the belief that information as to the outcome of treatment of the first 1400 cases in the Bladder Tumor Registry would be of value It will be recalled that there were two previous reports on the larger part of this material one in 1934, dealing with the analysis of cases, and one in 1936, with the results of a histologic and cytologic study The analysis of follow up information on these 1400 patients is presented in this paper

Since the material in this report is not entirely typical of the 6,000 cases in the Registry as a whole nor of a total population, the observations are valid only for this series

MATERIALS AND METHODS

The 1400 cases in this study have been selected from approximately the first 1600 entered in the Bladder Tumor Registry The 200 discarded were unsuitable for analysis for the following reasons specimens too degenerated to determine grade of tumor, 64, no tumor present in slides, 11, no slides available for review, 47, no clinical history, 2, tumors other than of bladder (erroneously entered in Bladder Tumor Registry), 16, duplicate cases, 4, cases removed for a combination of these reasons, 56

The series includes the 1224 cases that formed the basis of the 1936 report and an additional 176 cases, of which 168 were treated during or prior to 1936, and the remaining 8 in 1937 One fourth of the 1400 were treated during the years 1917 through 1927, and three fourths during 1928 through 1937 The cases finally chosen for the present study comprise 22 per cent of the tumors that were in the Bladder Tumor Registry at the end of 1950 and are not, as mentioned before, altogether representative of over 6,000 cases in the Bladder Tumor Registry

Three hundred and eighty four patients (27 per cent) were followed 5 years or longer, and of these 182 (13 per cent) were followed from 10 to 26 years after they were entered in the Registry

All tissue specimens were reviewed microscopically and re evaluated as to Registry grading by the staff of the Genito-urinary Pathology Section of the Armed Forces Institute of Pathology This was necessary because the cards giving Registry diagnoses used in the reports of 1934 and 1936 could not be located in 1951

Presented in part at annual meeting, American Urological Association, Chicago Ill May 21-24, 1951

* AFIP, Veterans Administration Central Laboratory for Pathologic Anatomy and Research

Coding of the data was done by professional statisticians in the Statistics Section, working in close collaboration with the Registrar. The numerically coded data were then transferred to machine records cards from which tabulations were made. The data were doubly checked and where tables were available from previous reports, these were compared.

Grading of the tumors. The diagnostic criteria used in the microscopic classification of these tumors were essentially those originally adopted by the Registry committee in 1927 and modified and simplified prior to 1940. The classification based on these criteria is as follows:

Grade I. Papillary carcinoma:* All papillary tumors with or without minimal anaplasia and disturbances of cellular arrangement, but with no evidence of infiltration of pedicle or bladder wall.

Grade II. Papillary, papillary and infiltrating, and sessile-nodular infiltrating: Tumors in which many of the cells are atypical in appearance, or the tumors of Grade I type that are larger than 2 cm. in diameter or are multiple or recurrent.† The tumors may or may not be infiltrating.

Grade III. Papillary and infiltrating, and sessile-nodular infiltrating: Tumors with marked anaplasia of cells, usually with invasion of the bladder wall, and often showing squamous metaplasia or pseudoglandular arrangement of the cells.

Less common forms of epithelial tumors of the bladder are the frank squamous cells carcinomas (that is, those that are squamous from the start) and the true adenocarcinomas of the bladder, many of which are mucus-containing. The latter group, which may arise in urachal remnants or as glandular metaplasia of the bladder epithelium, is the subject of a special study which will be reported later.

From the clinical point of view it is recognized that a classification of transitional cell tumors of bladder would be as follows:

Papilloma
Papillary carcinoma
Papillary and infiltrating carcinoma
Sessile-nodular infiltrating carcinoma

From the pathologist's point of view a simple classification of the epithelial tumors would be:

Papilloma
Carcinoma
Anaplastic carcinoma

No classification is entirely satisfactory as biologic processes do not always comply with the accepted concept of their behavior. The Registry classification has been subject to criticism because 1) it classifies all the epithelial tumors as carcinoma regardless of histologic evidence of malignancy; 2) it does not consistently base the grading of the carcinoma on histologic appearance of the tumor. This criticism is based on the fact that although the Registry does differentiate between Grade I, II and III on purely morphologic grounds, it also classifies as Grade II carcinoma all large (more than 2 cm), multiple and recurrent tumors, even if they are histologically of lower grade of malignancy

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* According to the custom of the Registry this term has come to mean transitional cell carcinoma and is distinguished from squamous cell carcinoma and adenocarcinoma.

† Since 1952 the diagnosis of Grade II carcinoma has been based solely on histologic appearance regardless of size, multiplicity or recurrence.

These criticisms are valid, but in answer to the first criticism, the Registry has maintained that since it is impossible by histologic methods to differentiate benign papillomas from those that recur and/or metastasize, the former should be classed as carcinoma so that neither the clinician nor the patient will look upon these tumors as completely harmless As for the second criticism, the Registry has claimed that the behavior of the recurrent, multiple and large tumors, even when such tumors are histologically benign, is indistinguishable from the behavior of epithelial tumors that are classed as Grade II carcinomas on purely morphologic grounds

When the 1400 cases were being re examined, the desirability of differentiating those which histologically appeared benign was considered The Registrar, however, was of the opinion that the Registry classification should be adhered to so that the data on this series could be compared with those for the remaining 4,000 or more cases in the Registry (no microscopic review of these cases is contemplated since the Registry diagnosis is available)

Uses and limitations of the data The Bladder Tumor Registry is less affected than are most of the other registries by the selective sex and age bias which exists in most of the material submitted to the Armed Forces Institute of Pathology, because comparatively few bladder tumors occur in men of military age As a matter of fact, 96 per cent of the 1400 cases were contributed by civilian physicians Because of this and the fact that during the late 1930's, Colonel James E Ash, then Curator of the Army Medical Museum, and members of his staff visited many of the contributors and collected both routine and problem cases, the material in the Bladder Tumor Registry is more nearly representative of those treated for bladder tumors in the total civilian population than would ordinarily be expected On the other hand, because a certain amount of selection was exercised when these tumors were taken from larger hospitals and clinics, neither the material at any one period nor the total is entirely representative of bladder tumor experience in everyday practice

ANALYSIS OF DATA

Items of information appearing on the Registry forms with sufficient frequency were coded for survey purposes

The pertinent general clinical data were as follows Of the 1400 patients, 1049 were dead, 287 were living at time of last follow up, and for 64 no information was available other than that at time of hospitalization

Of 1049 patients who were dead at the time of last known status, 196 (19 per cent) died at least 5 years or more after the time of treatment,* 813 (77 per cent) died within the 5 years following treatment, and in 40 (4 per cent) no information was available as to the interval before death Among the 196 who had died after

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* By treatment is meant the treatment that took place at the time of Registry admission By Registry admission is meant the examination which produced the first tissue specimen forwarded to the Armed Forces Institute of Pathology

TABLE 1. *Registry diagnoses of 1384 bladder tumors in relation to ages of patients*
Number

REGISTRY DIAGNOSIS	TOTAL	AGE GROUP (IN YEARS)			
		Under 30*	30–49	50–69	70–89
Total with age stated	1384	8	292	881	203
Papillary I	109	3	34	63	9
Papillary II	336	2	77	200	57
Papillary and Infiltrating II	322	—	67	204	51
Papillary and Infiltrating III	87	—	14	58	15
Infiltrating II and III	510	1	92	349	68
Others, not graded†	20	2	8	7	3

* Includes 4 patients 7 through 19 years of age and 4 aged 24 through 27 years.
† Includes 17 adenocarcinomas and 3 sarcomas.

surviving at least 5 years following Registry admission, 76 (39 per cent) had local recurrence, metastasis, or both; 67 (34 per cent) died from other causes, and 53 (27 per cent) with no details as to the status of the tumor. Of the 813 patients who died within the first 5 years, 535 (66 per cent) died with bladder tumor or metastasis or both, 61 (7 per cent) without bladder tumor or metastasis (presumably of other causes), and for 217 (27 per cent) the status of the tumor was not known. Among the 40 patients for whom no information as to the exact time of death was available, 10 died with bladder tumor and/or metastasis, one of other causes, and there was no information as to the status of the tumor in the remaining 29.

In summary, of the 1049 patients who were dead, 621 died with tumor, metastasis, or both, and 129 died presumably of causes other than cancer. Thus, of 750 deaths in which presence or absence of demonstrable tumor was fairly well established largely by clinical methods (not all the patients came to autopsy), tumors were recorded in 621, or 83 per cent. In the remaining 299 no information was available as to the presence or absence of the bladder tumor at the time of death.

Age. The ages of 1384 patients were recorded at the time of Registry admission. About two-thirds of the patients were from 50 through 69 years of age, a peak of incidence that corresponds well with reports in the literature. The youngest patients were 7 and 9 years of age,* the oldest 90 years.

Table 1 depicts the incidence of tumors by grade of malignancy in the different age groups. Statistical tests showed that the relative frequency of papillary tumors without infiltration was significantly higher in patients under 50 years of age than that of other graded tumors, while the more malignant tumors occurred among the older group.

Sex and race. The ratio of males to females, approximately 3 to 1 in our series, corresponds to that of Rauenbusch, and the proportion of males is slightly but apparently not significantly higher per 100 patients than the accepted pattern in the literature

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* The 7 year old child had sarcoma botryoides of the bladder and died 6 months postoperatively. The 9 year old girl, who had fibrosarcoma of bladder, was well for 10 years after operation, but has since been lost to follow-up.

Since the Registry forms did not provide for designation as to race, it was recorded for only 97 patients, 3 of whom were Negroes

Status of tumors at admission Thirteen hundred and eighty four (99 per cent) of the tumors were primary in the bladder Ten were metastatic from other organs, and in 4 others there was doubt as to whether the tumors were primary or secondary The remaining 2 were extensions to the bladder

The 10 secondary tumors do not include all cases at the Armed Forces Institute of Pathology in which there was metastasis to the bladder from tumors of other organs, but represent only those cases that have been entered in the Bladder Tumor Registry

Single tumors were present in the bladder in 1022 cases (73 per cent), and multiple tumors in 356 (25 per cent) In the remaining 22 cases (2 per cent) there was no statement as to number

Sites of tumors The location of 1363 of the tumors was either stated or indicated on the diagrams which appear on the Registry forms Of these, 19 involved the entire bladder Of the remaining 1344, 643 (48 per cent) were either single or multiple tumors but were in single areas of the bladder, their sites of vesical at-

TABLE 2 *Sites of origin of tumors involving single areas of the bladder*

SITE OF ORIGIN	NUMBER	PER CENT
Total	643	100
Trigone*	189	29
Vault	39	6
Bladder walls		
Anterior	37	6
Right lateral	144	23
Left lateral	149	23
Posterior	85	13

* Includes tumors in trigone, ureteral orifice and bladder neck

TABLE 3 *Primary sites of single tumors involving one or more areas of the bladder**

PRIMARY SITE	NUMBER	PER CENT
Total with data	993	100 0
Trigone†	504	51
Vault	66	7
Bladder walls		
Anterior	43	4
Lateral	307	31
Posterior	73	7

* Does not include 5 single tumors involving the entire bladder and 24 with location of the tumor not stated

† Includes tumors in trigone, ureteral orifice and bladder neck

TABLE 4 *Sites of origin of noninfiltrating and infiltrating carcinomas involving single areas of the bladder*

Number

SITES OF ORIGIN	TOTAL	NON-INFILTRATING PAPILLARY	INFILTRATING	
			Papillary	Non-Papillary
Total	637	247	176	214
Trigone*	187	72	55	60
Vault	36	5	13	18
Bladder walls				
Anterior	36	9	12	15
Right lateral	144	59	33	52
Left lateral	149	68	37	44
Posterior	85	34	26	25

* Includes tumors in trigone, ureteral orifice and bladder neck.

tachment are shown in table 2. A total of 993 were single tumors but had involved one or more known areas of the bladder. The primary sites of these tumors appear in table 3.

From these 2 tables it would seem that the trigone (including ureteral orifice and bladder neck) was the most frequent site of origin and/or involvement. Thirty per cent (i.e., 189) of the tumors involving single sites only and 51 per cent (i.e., 504) of all single tumors which involved one or more areas had originated in or involved the trigone. It should be noted that since table 3 includes the single sites which appear in table 3 the percentages in the 2 tables are not additive.

Sites of tumor in relation to diagnoses. Table 4 presents the primary sites of the tumors in 637 patients with carcinomas in known single areas of the bladder. This table is divided to show the percentage of infiltrating and noninfiltrating tumors in each location. Statistical tests indicate that in this group tumors in the vault were much more likely to be infiltrating. On further analysis it was found that only 4 per cent of all the papillary carcinomas (18 of 423) were in the vault as compared to 8 per cent of sessile-nodular carcinomas (18 of 214), a difference which appeared to be statistically significant (Chi-square = 4.604*). As suggested in a previous study (Rauenbusch), the vault is a "silent area" in which tumors are more likely to progress to malignancy before producing symptoms.

Four hundred and twenty-three (66 per cent) of the 637 tumors in single areas were of the papillary type. These included the 247 noninfiltrating and 176 of the 390 infiltrating tumors.

Previous occurrences of bladder tumors. One hundred forty-one (12 per cent) of

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* The Chi-square test for significance is used to test the reliability of the difference between two measures It measures whether the observed difference is larger than the difference which could be attributed to chance The result is applied to Pearson's "Tables for Statisticians and Biometricians" to determine its significance. The differences are considered statistically significant only when it could be shown that they might arise by chance in but 5 of 100 samples, or less frequently, that is, when the Chi-square is 3 841 or higher.

TABLE 5. *Principal types of treatment of 1312 patients with bladder tumor*

TYPE OF TREATMENT*	NUMBER	PER CENT
Total	1312	100.
Cystectomy	11	1.
Segmental resection	143	11.
Radon	620	47.
Excision and/or electrocoagulation	494	38.
X-ray alone	44	3

* Types of therapy represent selection in the order shown. Many patients had more than one form of treatment, but in each category are included only those patients who had none of the preceding types of therapy listed in the table

1175 patients for whom there was a record of presence or absence of previous lesions in the bladder were known to have had a bladder tumor. The frequency with which previous bladder tumors were reported in patients with tumors of different types and grades is as follows: 6 per cent of the patients with papillary tumors of Grade I, 13 per cent with papillary tumors of Grade II, 16 per cent with papillary and infiltrating tumors of Grade II. Eleven per cent of the patients in each of the remaining categories (papillary and infiltrating carcinoma, Grade III, infiltrating carcinoma, Grades II and III, and adenocarcinoma and sarcoma) had had previous tumors. Although the absolute rates of survival with or without reported recurrence or metastasis for tumors in different locations were probably modified by inclusion of patients with previous tumors, statistical tests indicated that the existence of a previous tumor had no significant effect on the relative tumor-free survival rates.

Types of therapy. The therapy employed was specified in 1312 (94 per cent) of the case records (table 5). Of the remaining 88, in 21 the tumors were inoperable and no treatment was given; for the other 67 there was no information other than that biopsy was performed.

In preparing this table the major types of therapy were selected. For example the 11 patients with cystectomy may have had any or all of the other types listed in the table. Similarly the 143 patients with segmental resection may have had any or all of the other types of therapy with the exception of cystectomy. In the 620 cases with radon implantation no open operation was performed, although excision or electrocoagulation and/or x-ray therapy may have been supplemental forms of treatment. In 252 (19 per cent) of these, however, radon implantation was the only method used. There are 31 cases, in addition to the 620, in which radon was used to supplement surgical procedures.

Similarly, the 494 patients treated by excision and/or electrocoagulation may have had x-ray therapy but none of the other types. Although roentgen radiation was the only method of treatment in 44 cases, it was used also in 98 additional cases in conjunction with other treatments.

Diagnosis in relation to type of therapy. A tabulation of the treatments in relation to the Registry diagnoses showed that resection, radon implantation and

TABLE 6. *Registry diagnoses in relation to types of treatment of 1312 patients with bladder tumor*
Number

DIAGNOSIS AND GRADE	TYPE OF TREATMENT*					
	Cystectomy	Resection	Radon	Excision†	X-ray	Total
Total . .	11	143	620	494	44	1312
Papillary I	—	2	37	65	1	105
Papillary II	2	22	136	160	6	326
Papillary and Infiltrating II	2	31	160	111	12	316
Papillary and Infiltrating III	2	17	34	26	4	83
Infiltrating II and III	5	66	247	129	20	467
Others‡	—	*5*	*6*	*3*	*1*	*15*

* Types of therapy represent selection in the order shown. Many patients had more than one form of treatment, but in each category are included only those patients who had none of the preceding types of therapy.

† Includes electrocoagulation.

‡ Includes adenocarcinomas and sarcomas.

x-rays were used more frequently for tumors of higher malignancy, while electrocoagulation or excision was the treatment of choice for almost two-thirds of the papillary tumors of Grade I (table 6).

Eleven simple cystectomies, all performed between 1931 and 1936, were included in the series. The ureters were transplanted to the skin in 10 cases and to the sigmoid colon in 1. Five postoperative deaths occurred; 3 other patients died within a year of operation, 2 with metastasis and 1 with no information regarding metastasis. One patient died 18 months after operation, but no information was given as to status of the tumor. One patient survived 3 years after treatment and died with pulmonary metastasis. The eleventh patient, aged 65 years, had had symptoms 2 years before cystectomy and cutaneous implantation of ureters. The specific site of the tumor, a papillary and infiltrating carcinoma, Grade III, was not recorded. The patient died 5 years postoperatively from a cerebral accident and there was no information concerning the presence or absence of tumor or metastasis at the time of death.

Pathologic diagnoses on the 11 cases were: infiltrating carcinoma, Grade III, 7; papillary and infiltrating carcinoma, Grade II, 2; and papillary carcinoma, Grade II (without infiltration), 2. It is noteworthy that the last mentioned tumors occurred in patients 32 and 40 years of age, whereas the other patients were between 55 and 68, inclusive.

In addition to these 11 cystectomies performed at the time of Registry admission, follow-up inquiries disclosed that 5 patients had had cystectomies following the admission treatment. Two patients had these operations within one year of admission (in 1925 and 1929); 2, seven years (1941 and 1944), and 2, seventeen years afterward (1948). Four of these patients died; 1 as a result of the operation and 3 after surviving for one year. The Registry diagnoses on these were papillary carcinoma, Grade II, in 2, papillary and infiltrating carcinoma, Grade II, in 1, and papillary infiltrating carcinoma, Grade III, in the fourth patient. The ureters were transplanted to the sigmoid colon in 2 cases and in 1 to skin. No mention was made of the ureters in the fourth case.

Of special interest was the fifth patient. In 1931, when he was 44 years of age, an *infiltrating carcinoma*, Grade III, was resected. He had at least 4 recurrences during the next 17 years, and at the end of this period transplantation of ureters into the sigmoid colon and total cystectomy, prostatectomy and seminal vesiculectomy were performed. He was last followed in 1950 when he was "alive and well," 2 years after total cystectomy and 19 years after the admission treatment in 1931.

Registry diagnoses as compared with contributors' diagnoses. A comparison of the Registry diagnoses with those of the contributors was made at the request of the Registry Committee because it was thought that the members of the American Urological Association would be interested in such a comparison. In 709 cases the contributors had not graded the tumors. In 691 the contributors had graded the tumors and a comparison of their diagnoses with those of the Registry is given in table 7. Since the Registry grades I to III, the 92 cases sent in as Grade IV were placed mostly in Grade III, with a small number in Grade II. In comparing the grading for the Grades I to III carcinomas it must be realized that histologic grading of the tumor is a matter of the examiner's opinion and the number of sections examined. Furthermore, it may vary on tissue specimens received from the same organ at different periods.

TABLE 7. *Comparison of the contributors' grading with that of the Registry**

CONTRIBUTORS' DIAGNOSIS	TOTAL	REGISTRY DIAGNOSES (AFIP)				
		Grade I	*Grade II*		*Grade III*	Adeno carcinoma
		Noninfiltrating	Noninfiltrating	Infiltrating	Infiltrating	
Total	691	41	164	187	293	6
Grade I†	166	35	86	40	4	1
Noninfiltrating	165	35	86	40	3	1
Adenocarcinoma	1	—	—	—	1	—
Grade II	206	4	58	84	59	1
Noninfiltrating	179	4	55	74	46	—
Infiltrating	3	—	—	1	1	1
Adenocarcinoma	24	—	3	9	12	—
Grade III	*227*	*2*	*12*	*55*	*154*	*4*
Noninfiltrating	170	2	12	51	104	1
Infiltrating	52	—	—	4	48	—
Adenocarcinoma	5	—	—	—	2	3
Grade IV	92	—	8	8	76	—
Noninfiltrating	71	—	6	7	58	—
Infiltrating	20	—	2	1	17	—
Adenocarcinoma	1	—	—	—	—	—

* Excludes 709 cases in which the contributors had not graded the tumors.

† Includes 65 designated as Papilloma, Grade I, and 101 as Carcinoma, Grade I.

There were 206 tumors sent in as carcinoma, Grade II, and 227 as carcinoma, Grade III. According to the Registry diagnosis, tumors placed in these two categories numbered 209 and 213, respectively—the small difference being due to assigning a few of the Grade III tumors to Grade II.

The only serious discrepancies between the contributors' diagnoses and those of the Registry were in the cases sent in as papilloma, ungraded, papilloma Grade I, papilloma Grade III, and carcinoma Grade I. There were 45, 65, 1, and 101 cases, respectively.

Analysis of cases sent in as carcinoma, Grade I. The Registry diagnoses on the 101 cases sent in as carcinoma, Grade I, expressed in percentages, are as follows: papillary carcinoma, Grade I, 21; papillary carcinoma, Grade II, 46; papillary and infiltrating carcinoma, Grade II, 27; papillary and infiltrating carcinoma, Grade III, 1; infiltrating carcinoma, Grades II and III, 4; and adenocarcinoma, 1. Ten of these patients were lost to follow-up, and 14 were dead without information as to the presence or absence of recurrence or metastases. One patient was alive without recurrence but is excluded because he had primary tumor elsewhere. Thus follow-up is recorded for only 76 cases. See table 8.

Thirty-one (40 per cent) of the patients died with tumor, metastases, or both, 30 per cent within 5 years; 4 were alive with tumor; and 41 were either alive or dead without tumor. Twelve of these patients, however, had had one or more recurrences between the time of admission and the last follow-up. Thus, 47 of the 76 patients had recurrence or died with tumor. The series is too small to permit reliable evaluation, but the Registry diagnosis seems to have reflected the outcome more accurately than the contributors' diagnosis.

TABLE 8. *Registry diagnoses of tumors in relation to survival data of 77 patients with tumors diagnosed as grade I carcinomas by contributors*

REGISTRY DIAGNOSIS (AFIP)	TOTAL NUMBER WITH DATA	LAST KNOWN STATUS* AND DURATION: PER CENT					
		Without Tumor		With Tumor			
		Alive or Dead		Alive		Dead	
		Under 5 Years	5 Years & Over	Under 5 Years	5 Years & Over	Under 5 Years	5 Years & Over
Total	77	27.	29.	2.	2.	30.	10.
Papillary							
Grade I	16	19.	56.	—	6.	13.	6.
Grade II	35	29.	23.	3.	3.	31.	11.
Papillary-Infiltrating							
Grade II	21	24.	23.	5.	5.†	29.	14.
Grade III	1	100.	—	—	—	—	—
Infiltrating							
Grades II and III	3	—	—	—	—	100.	—
Adenocarcinoma	1	—	—	—	—	100.	—

* Excludes 10 patients who could not be followed and 14 patients dead with no information as to recurrence or demonstrable metastasis.

† This patient was alive without recurrence but with a primary tumor elsewhere.

TABLE 9. *Registry diagnoses of tumors in relation to survival data of 82 patients with tumors diagnosed as papillomas by contributors*

REGISTRY DIAGNOSIS (AFIP)	TOTAL NUMBER WITH DATA	LAST KNOWN STATUS* AND DURATION: PER CENT					
		Without Tumor		With Tumor			
		Alive or Dead		Alive		Dead	
		Under 5 Years	5 Years & Over	Under 5 Years	5 Years & Over	Under 5 Years	5 Years & Over
Total	82	15.	50.	2.	2.	22.	9.
Papillary							
Grade I	24	21.	50.	8.	—	13.	8.
Grade II	38	11.	63.	—	3.	18.	5.
Papillary-Infiltrating							
Grade II	16	19.	31.	—	6.†	25.	19.
Grade III	1	—	—	—	—	100.	—
Infiltrating							
Grades II and III	2	—	—	—	—	100.	—
Adenocarcinoma	1	—	—	—	—	100.	—

* Excludes 6 patients who could not be followed, 22 patients with no information as to recurrence or demonstrable metastasis and 1 patient with Grade III papilloma.

† This patient was alive without recurrence but with tumor in another organ not specified as metastatic.

Analysis of cases with contributors' diagnosis of papilloma. In the first 1400 bladder tumors there were 111 for which the contributors' diagnosis was papilloma; 66 Grade I papilloma, 1 Grade III papilloma, and 45 papilloma. The Registry grading on these cases in 1951 was as follows: 29 carcinoma, Grade I; 52 carcinoma, Grade II, and 30 carcinoma, Grade III. It should be emphasized that the grading was done without reference to the follow-up information which was not available to the pathologist. See table 9.

In analyzing these cases it must be realized that the term papilloma may sometimes have been used rather loosely and not all the tumors may have been considered entirely benign by the contributor, as the diagnosis of papilloma would imply. As a matter of fact, the case sent in as papilloma, Grade III, was deleted from this analysis since the diagnosis was obviously intended to be carcinoma. Of the remaining 110, which is again admittedly too small for any reliable evaluation of the Registry grading, another 28 had to be dropped: 6 patients lost to follow-up and 22 without any information as to recurrence or metastases.

Table 9 presents the Registry diagnoses in relation to the last known status of the remaining 82 patients. It will be noted that 25 of the 82 patients with the contributors' diagnosis of papilloma were dead with tumor, 18 within 5 years. Four patients were alive with tumor, and 53 were living or dead without tumor, 12 of these less than 5 years, and 41, 5 years or over. It should be noted, however, that of the 53 patients living or dead without tumor at the time of last follow-up, 21 had had one or more recurrences in the interim between the admission tumor and the last known status. Thus, of the 82 patients with the contributors' diagno-

TABLE 10. *Registry diagnoses of the first 1400 cases in the bladder tumor registry*

DIAGNOSIS	NUMBER	PER CENT
Total	1400	100.
Papillary carcinoma	867	62.
Non-infiltrating	450	32.
Infiltrating	417	30.
Sessile-nodular carcinoma	513	37.
Adenocarcinoma	17	1.
Sarcoma	3	

sis of papilloma, 21 had had one or more recurrences, 4 were alive with tumor, and 25 were dead with tumor—a remarkable outcome for a supposedly benign tumor! The Registry diagnoses in this series, small as it is, seem to have offered a better prognostic index than the contributors' diagnoses.

Registry diagnoses. See table 10. Eight hundred sixty-seven (62 per cent) of the tumors were papillary, almost evenly divided between noninfiltrating (450) and infiltrating types (417); and 513 (37 per cent) sessile-nodular, infiltrating. The 417 papillary and infiltrating carcinomas included 330 carcinomas, Grade II, and 87 carcinomas, Grade III. Twenty were ungraded tumors, 17 diagnosed as adenocarcinoma and 3 as sarcoma.

It is of interest that the percentage of papillary tumors (62 per cent) is higher than that obtained for the first 921 cases included in the 1934 report. There, 48 per cent of the tumors were classified as papillary. In the current analysis, as yet incomplete, of almost 6,000 bladder tumors in the Registry, the papillary tumors comprise 75 per cent of the total. Thus, in the cases that were received in the Registry up to 1936, the percentage of papillary tumors is distinctly lower than the generally reported incidence of 75 to 90 per cent.

Cellular types of carcinomas. See table 11. In this presentation there was no attempt to make a detailed study of the cellular type, as was done in 1936. Indeed, the main effort was to grade the tumors. Ninety-six per cent of papillary carcinomas and 59 per cent of sessile-nodular carcinomas were transitional. The number of papillary tumors showing foci of squamous cells or squamous cell

TABLE 11. *Cellular types of 1380 epithelial tumors**

CELL TYPE	TOTAL	
	Number	Per Cent
Papillary carcinomas		
Total	867	100.
Transitional	835	96.
Squamous or squamous cell tendency	32	4.
Sessile-nodular carcinomas		
Total	513	100.
Transitional	304	59.
Squamous cell tendency	209	41.

* Excluding 17 adenocarcinomas and 3 sarcomas.

carcinoma (32, or 4 per cent), although in essential agreement with previous Registry reports on these cases, may be somewhat less than would be the case had multiple sections of each tumor been available for study.

Also not mentioned in the table is the tendency of about one-fifth of the sessile-nodular carcinomas to form pseudoglandular areas. These and other cellular changes will be the subject of subsequent studies.

SURVIVAL RATES AND RATES OF SURVIVAL WITH NO REPORTED TUMOR

Survival rates and rates of survival without indication of tumor are presented in this report. The survival rate is calculated by the direct method, and shows the percentage of patients who were alive or dead at the time of last follow-up. The rate of survival for specified periods after treatment without reported indication of tumor is sometimes referred to in the literature (Martin, MacComb and Blady; Berkson and Gage) as "5, 10, or 15-year cure rate." This rate measures, to some extent at least, the length of survival without evidence of recurrence, new tumor in the bladder, or metastasis from the bladder tumor.

For greater accuracy in computing the survival data, patients who died without information as to tumor status are excluded, as are those patients who could not be followed for lack of sufficient identifying information. The assumption made by the exclusion is that the behavior of these patients was similar to that of the patients for whom complete information was available.

Computation of the rate of survival without indication of tumor requires inclusion of all patients who survived for a stated period, with classification as "failures in treatment" of all who had a primary tumor in the bladder or demonstrable metastasis from this tumor at any time between treatment and the period selected. Therefore, those patients who survived for the specified periods without demonstrable bladder tumors or metastasis are classified as "reported tumor-free."

Survival data. The percentages of patients alive or dead at last follow-up and

TABLE 12. *Registry diagnoses of tumors in relation to survival data of 1296 patients**

REGISTRY DIAGNOSIS	TOTAL NUMBER OF PATIENTS WITH DATA	LAST KNOWN STATUS AND DURATION; PER CENT			
		Alive		Dead	
		Under 5 Years	5 Years & Over	Under 5 Years	5 Years & Over
Total	1296	8.	14.	63	15.
Papillary					
Grade I	98	17.	41.	20	22
Grade II	311	12.	28	37	23
Papillary and Infiltrating					
Grade II	306	8.	12	63.	17
Grade III	82	4.	6.	80	10.
Infiltrating					
Grades II and III	480	3	4	84	9.
Others†	19	—	5	84.	11.

* Excludes 64 patients who could not be followed and 40 patients with no stated duration.
† Includes adenocarcinomas and sarcomas.

TABLE 13. *Five-year reported tumor-free* rate of 1004 patients with bladder tumors*

LAST KNOWN STATUS	NUMBER
Total patients in series	1400
"Indeterminate" group	396
"Determinate" group	1004
Treatment failures	838
Died with tumor, metastasis, or both	725
Living with tumor, metastasis, or both	113
Good results after 5 or more years	
Reported free from tumor or demonstrable metastasis	166
Five-year end-results	
Reported tumor-free cases divided by "determinate" group (166/1004)	17%

* No reported indication of demonstrable tumor or metastasis.

the length of survival for each diagnostic group are shown in table 12. The decreasing percentages of patients who survived with or without tumor 5 years or longer as the degree of malignancy increased is well illustrated. In other words, the percentage of patients dying within 5 years increased in direct relation to higher grades of malignancy.

Rates of survival without tumor. The 5-year rate of survival with reported freedom from subsequent bladder tumor or metastasis is shown in table 13. The 1400 patients in the series were divided into two groups: the "indeterminates," those without follow-up or without details as to presence or absence of recurrent or metastatic tumors; and the "determinates," those with definite information as to disease status. Definite information was available for 1004 patients (the "determinate" group), who were then classified as representing either treatment failures or treatment successes for the period specified. The "5-year failures" comprised 83 per cent; 626 (62 per cent) who died within 5 years with (not necessarily of) tumors; 99 (10 per cent) who died after 5 years and 113 (11 per cent) who, although living after 5 years, had tumors within 5 years after operation. The remaining 166 (17 per cent) represented good results of treatment at the 5 year interval, since there was no evidence of disease.

"Tumor-free" rates. See table 14. The Registry diagnoses of bladder tumor in the 1004 "determinate" patients were considered for each diagnostic group in relation to "tumor-free" results 5, 10 and 15 years or more after admission. At each of the longer intervals the "determinates" were decreased by the number of patients lost to follow-up between intervals. Thus, while the 5 year rates are based on 1004 cases, those for 10 years are based on 944 and for 15 years on 895.

The consistency of data on survival rates and on rates of survival with no reported indication of tumor for stated periods indicates that the current Registry grading affords an excellent prognostic index for tumors of the urinary bladder. In general, the rates of "tumor-free" survival decrease with increasing degrees of malignancy, as does the survival rate. A subsequent study of some 2600 patients, in which the percentages of "tumor-free" patients among the survivors in each diagnostic group were computed, indicates that although comparatively

TABLE 14. *Registry diagnoses of 1004 bladder tumors in relation to reported "tumor-free"* rate at 5, 10 and 15 or more years after admission*

REGISTRY DIAGNOSIS AND GRADE	TOTAL DETERMINATE CASES	"TUMOR-FREE" RATES		
		Duration from Admission		
		5 yrs †	10 yrs †	15 yrs & over†
Total with data	1004	166	94	45
Per cent of total		17.	10	5
Papillary				
Grade I	73	37.	23	10.
Grade II	284	27	17	7.
Papillary and Infiltrating				
Grade II	238	15	9.	5.
Grade III	63	10.	6.	—
Infiltrating				
Grades II and III	364	8.	5.	3.
Others‡	18	11	6.	—

* No reported indication of demonstrable tumor or metastasis

† Five-year rates based on 1004 patients with data; 10-year rates on 944, and 15-year rates on 895

‡ Includes adenocarcinomas and sarcomas.

very few patients with the more malignant tumors survive for an appreciable length of time, the majority of those who do survive for 10 or 15 years are reportedly free from recurrent or metastatic tumors after initial definitive treatment.

Type of therapy in relation to "tumor-free" rates. An attempt was made to evaluate the 5-year "reported tumor-free" survival rates in relation to the grades of tumors and to the type of treatment on admission. Since some of the patients had received treatments prior to those for which the Armed Forces Institute of Pathology received the first tissue specimen (admission treatment), it was recognized that the previous treatments as well as those at admission might affect the 5-year rates to some extent.

The total "determinate" cases, that is, those with definite information regarding microscopic diagnosis, admission treatment, and presence or absence of tumor or metastasis 5 years after the Registry admission, numbered 906. In each diagnostic group the rate of "tumor-free" survival was computed for tumors treated by: 1) use of radon alone or radon with any other type of treatment except cystectomy, 2) resection alone or resection with excision, electrocoagulation, or x-rays; and 3) excision, electrocoagulation, or x-rays, separately or in combination. Analyzed on this basis, no type of treatment appeared more successful than another. As table 15 indicates, radon implantation alone or radon seeds in addition to surgical treatment appeared to produce no significantly higher proportion of reported symptom-free 5-year survivors than when radon was not used.

This table does not include the 11 cases with cystectomy which were previously discussed. Radon implantation was used in 2 of these, in 1 at the time of a suprapubic cystotomy preceding the cystectomy.

TABLE 15. *Registry diagnosis and treatment of 906 epithelial bladder tumors in relation to five-year reported "tumor-free"* rate*

DIAGNOSIS, GRADE AND TREATMENT	TOTAL DETERMINATE CASES	FIVE-YEAR "TUMOR-FREE" RATE
Papillary I		
Radon alone or with others	27	41.
Resection alone or with others (except radon)	—	—
Excision, electrocoagulation and/or x-ray	41	39.
Papillary II		
Radon alone or with others	101	29.
Resection alone or with others (except radon)	14	29.
Excision, electrocoagulation and/or x-ray	122	26.
Papillary and Infiltrating II		
Radon alone or with others	119	17.
Resection alone or with others (except radon)	19	16.
Excision, electrocoagulation and/or x-ray	88	14.
Papillary and Infiltrating III		
Radon alone or with others	27	19.
Resection alone or with others (except radon)	11	—
Excision, electrocoagulation and/or x-ray	22	5.
Infiltrating II and III		
Radon alone or with others	170	11.
Resection alone or with others (except radon)	42	12.
Excision, electrocoagulation and/or x-ray	103	6.
Total	906	18

* No reported indication of demonstrable tumor or metastasis.

TABLE 16. *Sites of origin of bladder tumors involving single areas in relation to five-year reported "tumor-free"* rate*

SITE OF ORIGIN	TOTAL DETERMINATE CASES	FIVE-YEAR "TUMOR-FREE" RATE
Total	476	27.
Trigone†	135	21.
Vault	34	21.
Bladder walls		
Anterior	26	35.
Right lateral	111	26.
Left lateral	111	37.
Posterior	59	22.

* No reported indication of demonstrable tumor or metastasis.
† Includes tumors in trigone, ureteral orifice and bladder neck.

Sites of origin of tumors in relation to "tumor-free" rates. Table 16 is based on 476 of the 643 tumors in single sites for which both location and 5 year status were known. When the percentage of tumors in each of the single sites was related to a 5 year symptom-free survival after treatment, there appeared to be no significant relation between location and subsequent freedom from tumor.

Disease status after admission. See table 17. "Disease status" as used in this

TABLE 17 *Disease status of 1106 patients from registry admission to last follow up**

DURATION FROM ADMISSION	TOTAL NUMBER PATIENTS WITH DATA	LAST KNOWN STATUS					
		Per Cent					
		No Tumor or Metastasis			Tumor and/or Metastasis		
		Total	Living	Dead	Total	Living	Dead
Total with status known	1106	23	15	8	77	10	67
Less than 1 year	384	6	2	4	94	2	92
1 to 5 years	358	22	14	8	78	8	70
5 to 10 years	171	35	21	14	65	21	44
10 to 15 years	99	49	37	12	51	24	27
15 years and over	72	57	44	13	43	26	17
Duration not stated	22	—	—	—	100	—	100

* Excludes 64 patients who could not be followed and 230 for whom the status of tumor at last follow up was not determined.

report refers only to recurrence of the bladder tumor or metastasis from tumor of the bladder.

Data were available as to the disease status of 1106 patients at the time of death or during their survival for various periods after the Registry admission. These figures include the 21 patients with inoperable tumors who received no treatment and died with the admission tumor and, in most instances, with metastasis also.

At some time following admission treatment 854 (77 per cent) of the 1106 patients had bladder tumors, metastasis, or both. In 740 (67 per cent) it was known that the lesion had been present between admission treatment and time of death, although in 119 it was reportedly not present at death. The remaining 252 (23 per cent) were reportedly free of metastasis and/or tumor between treatment and last follow up. Eighty nine of these 252 patients died without tumor or demonstrable metastasis. These were patients who died of causes other than the bladder tumor, although the bladder lesion may have contributed to death. The remaining 163 patients were living without known bladder tumor and/or metastasis.

The duration from admission to last known status was reported for 1084 of the patients. Table 17 shows the status of these patients at the time of the last report, regardless of whether there had been recurrence of tumor during the interim. Among the 384 patients followed less than 1 year, only 6 per cent appeared to be free from both tumor and metastasis. The proportions in this favorable category increased sharply thereafter, so that of 99 patients followed 10 to 15 years after the admission treatment, 49 per cent were reported free from bladder tumor or metastasis, and of 72 with information 15 through 25 years after admission, 57 per cent had no demonstrable tumor or metastasis. Probably the actual tumor status of these patients was considerably better than that reported.

In each tumor group, metastatic lesions were most frequently found within 5 years after admission. There were records of 2 patients with infiltrating carcinomas of Grade III who showed no evidence of metastasis for more than 10 years

These were re-examined for possible error, but it was found that in each case the physicians who replied to yearly or biannual follow-up inquiries had frequent contacts with the patient and made repeated clinical examinations. In the first case, follow-up reports at frequent intervals for nearly 16 years were negative for both recurrence and metastasis, but at death metastatic lesions were reported in the right anterior fifth rib and posterior chest wall. There was no record as to whether autopsy was performed. In the second case, invasion of the prostatic urethra was reported within 4 years. After deep x-ray therapy and dilatation of the urethra the patient was apparently symptom-free, and 10 years after admission the cystogram revealed no evidence of a bladder tumor. However, benign prostatic hypertrophy was reported. Two years later suprapubic prostatectomy was performed and no bladder tumor was seen. At time of death 3 years later (15 years after admission) there was an extensive infiltrating sessile tumor (squamous cell carcinoma) and metastatic lesions involving the symphysis pubis, abdominal wall, and regional lymph nodes.

Metastasis. Each diagnostic group was studied in relation to the presence or absence of metastasis subsequent to the admission treatment. The result is shown in table 18. It must be emphasized, however, that the Registry data on incidence and location of metastatic lesions were not entirely satisfactory because they were based on clinical examination. Accurate data based on complete autopsy reports were available in only a small percentage of cases and in many others the available data were so meager as to cast doubt on their accuracy.

Metastasis was recorded for 188 (17 per cent) of the 1106 patients. In 15 per cent metastases appeared within 5 years after the admission treatment, in 1 per cent they were found between 5 and 10 years, and in 1 per cent more than 10 years after admission treatment.

The relative incidence of metastases increased strikingly with tumors of a higher degree of malignancy. Among patients with infiltrating tumors of Grade

TABLE 18. *Registry diagnoses in relation to metastasis from bladder tumors at last known status of 1106 patients**

REGISTRY DIAGNOSIS AND GRADE	NUMBER OF DETERMINATE CASES	PER CENT WITH METASTASIS			
		Total	Duration from Admission		
			Under 5 Years	5 to 10 Years	10 Years and Over
Total	1106	17.	15.	1.	1.
Papillary I	87	3.	2.	1.	—
Papillary II	285	8.	4.	2.	2.
Papillary and Infiltrating II	260	15.	12.	1.	2.
Papillary and Infiltrating III	67	27.	27.	—	—
Infiltrating II and III	389	25.	22.	2	1
Others†	18	50.	50.	—	—

* Data based on statements made by examining physicians and not on complete autopsy findings.

† Adenocarcinomas and sarcomas

II and Grade III, metastases appeared nine times as frequently as in those with papillary tumors of Grade I, and more than three times as frequently as those with Grade II papillary tumors Most of the metastases in these groups were present within the first 5 years

Metastatic lesions were demonstrated in a significantly higher percentage (91 per cent) of the patients with infiltrating tumors within 5 years than in those with noninfiltrating tumors (52 per cent) Thus, of 372 "determinate cases" with noninfiltrating tumors, only 25 were reported as having metastatic lesions, with 13, or 52 per cent, of these occurring within 5 years after the Registry admission In contrast, of 734 "determinate cases" with tumors of the infiltrating type, 160 had demonstrable metastases, and 146 (91 per cent) of these were observed within 5 years The Chi square value (27 57) indicates that the difference is real, rather than the result of chance in sampling

SUMMARY

Restudy of the first 1400 cases in the Bladder Tumor Registry, all except 8 received prior to 1937, reveals that of 1004 patients for whom information was available, 725 died (626 within 5 years) with tumor, metastases or both, 113 were living with tumor, metastases or both, and that only 166 were reported free from tumor or demonstrable metastases at the end of 5 years

The Registry classification, although inconsistent from the pathologic point of view, offers a good prognostic index of the behavior of epithelial tumors of the bladder In general, the rates of survival without demonstrable tumors of the bladder or metastatic lesions decreased with increasing degrees of malignancy, as did the survival rate

The prognosis of the infiltrating carcinoma was distinctly less favorable than that of the noninfiltrating papillary carcinoma

In 906 of these 1400 patients a comparison of cases treated by radon with those treated by other methods (exclusive of radon) showed no appreciable difference in the outcome

CONCLUSIONS

It must be realized that all but 8 of the patients presented in this study were treated prior to 1937 The discouraging results reflect the limitations that existed before that year, namely, late diagnosis and absence of chemotherapeutic and other agents for proper control of infection

Whether the outlook for patients with bladder tumor has changed with recent advances in diagnosis and therapy may become evident when bladder tumors received in later years are studied Conclusions should, therefore, await comparison of the data from the current study with those of subsequent periods

ACKNOWLEDGMENTS

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THE ILEOCECAL SEGMENT AS A SUBSTITUTE BLADDER
A REVIEW OF 18 CASES

JAMES W MERRICKS AND R K GILCHRIST

From the Rush Departments of Urology and Surgery, Presbyterian Hospital, Chicago, Ill in affiliation with the University of Illinois College of Medicine

This is a report of 18 patients in whom a substitute bladder and urethra was constructed as described by us 3½ years ago[1] Sixteen were operated upon for malignant disease, one for urinary incontinence due to congenital spinal cord defect and exstrophy of the bladder[2] and another for eosinophilic granuloma of the bladder Six of the sixteen cancer patients had no chance of surgical cure of their malignancies (table 1) These included 2 cases of carcinoma of the prostate, two of carcinoma of the cervix, one carcinoma of the bladder and one pararectal sarcoma Of those with possibility of cure, there were five infiltrative carcinomas of the bladder and five carcinomas of the cervix (table 2)

STAGES OF SURGERY

Where palliation only was attempted, the bladder was constructed and the ureters implanted at the same time In the 10 patients where surgical cure was attempted, usually the bladder was constructed, the pelvic exenteration done and then the ureters implanted into the new bladder in one operation Pelvic exenteration was done only in the cases of carcinoma of the cervix

Cystectomy with node dissection was performed in the carcinomas of the bladder Seven of the ten patients with bladder and uterine carcinoma had had previous abdominal operations for their neoplastic diseases

MORTALITY

One of the 6 cases done for palliation died of perivesical abscess and septicemia several weeks postoperatively following transurethral fulguration of the hemorrhaging sloughing bladder tumor The kidneys were in remarkably good condition and the new bladder had functioned perfectly The other five patients were all dead within 2 years (table 3)

Of the 10 patients where cure was attempted, three died in the postoperative hospitalization period The first, a man aged 64, carcinoma of the bladder, was very obese with arteriosclerotic heart disease and cirrhosis of the liver Bowel preparation caused extreme fluctuations in the prothrombin time The bladder was constructed with great difficulty, the ureters were not transplanted Death occurred on the twelfth postoperative day Necropsy revealed peritonitis with pulmonary metastasis The second death occurred in a man, aged 49, carcinoma of the bladder One kidney had been removed elsewhere because of ureteral obstruction, secondary to transurethral fulguration Cystectomy was very difficult

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Read at annual meeting American Urological Association, St Louis Mo May 13, 1953

[1] Gilchrist R K Merricks, James W Hamlin, H H and Rieger I T Construction of a substitute bladder and urethra Surg Gynec & Obst , 90 752-760, 1950

[2] Rieger I T and Weisser J R Substitute bladder operation on a paraplegic U S Armed Forces Med J 3 1507 1513, 1952

TABLE 1. *Total cases, 18*

Cancer	16	Benign	2
A. Palliation	6		
B. Chance for cure	10		

TABLE 2

	CASES
A. Palliation	
Ca. of prostate	2
Ca. of cervix	2
Ca. of bladder	1
Sa. of pararectal	1
	6
B. Chance for cure	
Ca. of bladder	5
Ca. of cervix	5
	10

TABLE 3. *Deaths*

A. Palliation	6	
Postoperative		1
Within 2 years		5
B. Control	5	
Postoperative		3
Within 18 mos.		2

due to perivesical adhesions. Leakage occurred 48 hours postoperatively, at which time the only ureter was retransplanted. Fluid balance was difficult to maintain, but output was adequate the first few days, when anuria developed following removal of the inlying ureteral catheter which was inserted at the time of reimplantation. Nephrostomy was not performed because the clinical impression was that of urinary suppression. However, the necropsy showed an angulation of the ureter, but no dilatation of the ureter or pelvis. The terminal nonprotein nitrogen was 68, NaCl 85 mEq/L, CO2 34.2 mEq/L. The kidney weighed 250 gm. and showed only mild tubular nephrosis. Henceforth, in a patient with a single kidney we plan to make the bladder and implant the ureter at the first operation and remove the pelvic organs two or three weeks later.

The third death occurred in a woman aged 48, with carcinoma of the cervix. She received 50 transfusions, mostly preoperatively. Death occurred on the seventy-fourth postoperative day of viral hepatitis. Terminal chemistry studies were normal and the new bladder had been quite satisfactory. Two additional patients [illegible] 18 mon[illegible] [illegible]gery. One, a man, aged 74, who prior to cystect[illegible] [illegible]nstruction [illegible] [illegible]cecal bladder (done on May 22, 1950) had a combined abdominal perineal resection of the rectum for carcinoma by one of us (R K G) in 1941 and suprapubic prostatectomy elsewhere in 1943 Laparotomy for intestinal obstruction was done by us 5 days following cystectomy

This patient has been reported by Creevy,[3] but his account does not present all of the important factors which resulted in this patient's death The following is taken from the postmortem protocol sent us by Dr I D Baronofsky[4] who was responsible for the patient's care Laparotomy for intestinal obstruction was done on Dr Baronofsky's service in the Ancker Hospital, St Paul, Minn about six months after cystectomy At that time (November 27, 1950) blood chemistry values were blood urea nitrogen 9 8, CO_2 combining power 65 vol per cent, Cl 470 mg per cent, indicating a lack of hyperchloremic acidosis Three months later on March 26, 1951 the blood urea nitrogen was 21, CO_2 combining power 58, Cl 626, and on March 29, 1951 the blood urea nitrogen was 15 4 On May 14, 1951 they attempted to close an abdominal fistula but fecal drainage continued The urine became grossly purulent at about this time On June 1, 1951 an ileocolostomy was made The ileum was sectioned 12 inches proximal to the fistula The distal end of the sectioned ileum was inverted The proximal end was anastomosed to the transverse colon Following this the patient had severe and constant diarrhea His course from then on was stormy The fistula began to drain again His course was steadily downhill and he died on January 14, 1952, having had a very severe chemical imbalance

The postmortem examination showed that "at a point 250 cm distal to the ligament of Treitz there is an end to side anastomosis of the small intestine to the transverse colon The stoma is adequate The balance of the small intestine is collapsed and the distal small intestine is densely adherent to the anterior and lateral abdominal wall low down in the left lower quadrant of the abdomen Here there is an external fistula of the small intestine, the opening of which is described above " The kidneys showed moderate pyelonephritis Does it not seem likely that this man who previously had a competent bladder, no sign of chemical imbalance or pyelonephritis, died of chemical imbalance as a result of the operation for intestinal obstruction? His functioning intestinal tract consisted only of 250 cm of jejunum, the left half of the transverse colon, the descending colon and about half of the sigmoid The resulting persistent diarrhea plus absorption from a blind loop of several feet of terminal ileum probably were as responsible for his severe chemical imbalance as the mild pyelonephritis

The other patient (carcinoma of the cervix) expired within a year of unrelated cardiac disease She was quite satisfied with her bladder function

SURVIVORS

In the cancer control group, five patients or 50 per cent are living and carrying on their normal activities from 10 to 26 months after surgery In the benign group,

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[3] Creevy C D and Reiser M P Observations upon the absorption of urinary constituents after ureterosigmoidostomy the importance of renal damage Surg , Gynec & Obst , 95 589–596 1952

[4] Baronofsky, I D Personal communication, 1952

TABLE 4. *Survivors, total 7*

Ca. Control	5	Benign	2
26 Mos.	1	24 Mos.	1
21 Mos.	1	13 Mos.	1
14 Mos.	1		
12 Mos.	1		
10 Mos.	1		

one is known alive at 13 months, the other is known to have survived 24 months (table 4).

Case abstracts of the living in the cancer control group are as follows:

Case 1. Mrs. F. C., aged 47, No. 516305, had extensive recurrent carcinoma of the cervix with vesicovaginal fistula. Preoperative chemistry was normal. Preoperative excretory urogram showed a right duplicated ureter. Ileocecal bladder was constructed as the first stage March 21, 1951; patient was extremely obese. Cystectomy with removal of cervix and nodes containing cancer about the aorta at the origin of the right ovarian vessels as well as the usual pelvic distribution were done and three ureters were transplanted April 28, 1951, as the second stage. Postoperative excretory urogram January 18, 1952 showed mild dilatation of all three ureters. Bladder capacity was 300 to 500 cc; patient was continent. Abdominoperineal resection of rectum, stump of vagina and labia majora was done on August 28, 1952. Blood chemistry August 30, 1952 was Na 138 mEq/L, K 4.2, NaCl 94, CO2 26.6 mEq/L. She is well today 26 months after surgery.

Case 2. Miss H. R., aged 50, No. 524192, had recurrent carcinoma of the cervix. Preoperative excretory urogram is shown in figure 1, *A*. Construction of ileocecal bladder, pelvic evisceration and colostomy were done August 8, 1951. A hard, stiff catheter was pushed through the cecal pouch on the ninth postoperative day, following which all urine drained through the perineal wound. A soft catheter with many openings was placed in the pouch and continuous suction applied for 9 days, at which time the perforation had healed. Postopera-

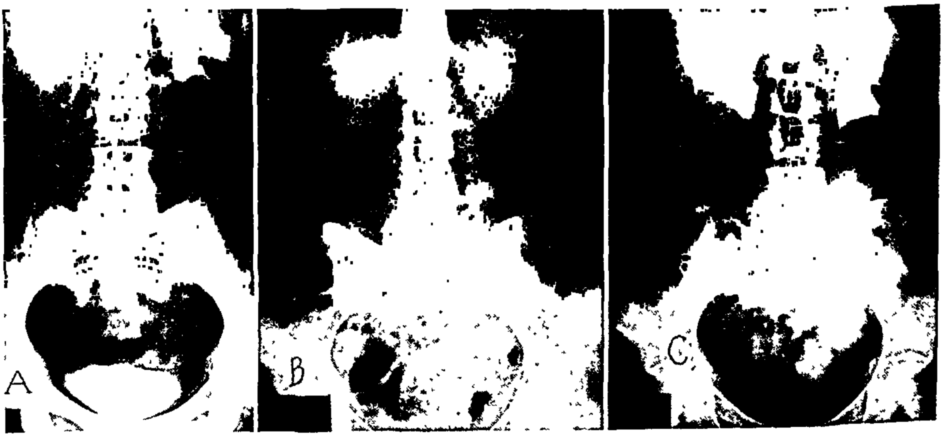

FIG. 1. Case 2. *A*, preoperative excretory urogram. *B*, plain film of abdomen 20 months postoperative. Note suspicious shadows in bony pelvis. *C*, excretory urogram 20 months postoperative. Cystoscopy showed no calculi in new bladder.

tive cystoscopy of bladder was done October 2, 1952, capacity was 350 cc, patient was continent, blood chemistry values were nonprotein nitrogen 31, NaCl 101 mEq/L, CO2 26 1 mEq/L Postoperative excretory urogram March 19, 1953 showed questionable bladder calculi (fig 1, *B* and *C*) Ileocecal cystoscopy April 28, 1953 showed no calculi The patient states that the new bladder is easier to care for than the colostomy She is well now at 21 months after surgery

Case 3 Mrs M W , aged 38, No 537954, had recurrent carcinoma of cervix and extensive vesicovaginal fistula Preoperative excretory urograms March 19, 1952 revealed slightly dilated ureters Construction of ileocecal bl hysterectomy, cystectomy and node dissection were done March 29, Sigmoid colostomy for rectovaginal fistula was necessary May 14, 1952 ing pelvic abscess Blood chemistry was normal on May 23, 1952 On Dec 9, 1952 the nonprotein nitrogen was 31, Cl 540, CO_2 combining 15 Good b capacity with continence was achieved Postoperative retrograde cystog 3 months revealed right ureteral reflux (fig 2) Postoperative excretory ur at 7 months revealed moderate bilateral hydronephrosis. This is the on

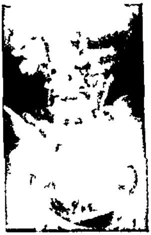

FIG 2 Case 3 Retrograde cystogram 3 months postoperative Note right ureteral This is only reflux found in living patient

teral reflux we have seen in the living patient Her mild acidosis is con by drachms one NaHCO3 t i d She is on an unlimited diet 14 month operatively

Case 4 Mrs G E , aged 64, No 542244, had recurrent multiple tun the bladder after segmental resection of bladder for tumor by Dr H L schmer on July 10, 1950 An old history of thrombophlebitis was elicited struction of substitute bladder, hysterectomy and cystectomy were don 17, 1952, pelvic tissues wept constantly Preoperative excretory urogr vealed a normal upper urinary tract Postoperative urograms at 6 month normal Postoperative blood chemistry Nov 5, 1952 was NaCl 103 n CO2 26 6, and nonprotein nitrogen 25 She now has recurrence in the stump Bladder capacity is 200 cc and she spills urine only when excite

Case 5 Mr S M , aged 42, No 545796, had an infiltrating tumor ab plicated ureteral orifices on the right Hematuria occurred once 3 wee viously A cecal bladder was constructed and cystectomy with node re were done July 30, 1952 Preoperative excretory urogram showed compl plication of the right ureter (fig 3, *A*) New bladder capacity was 400

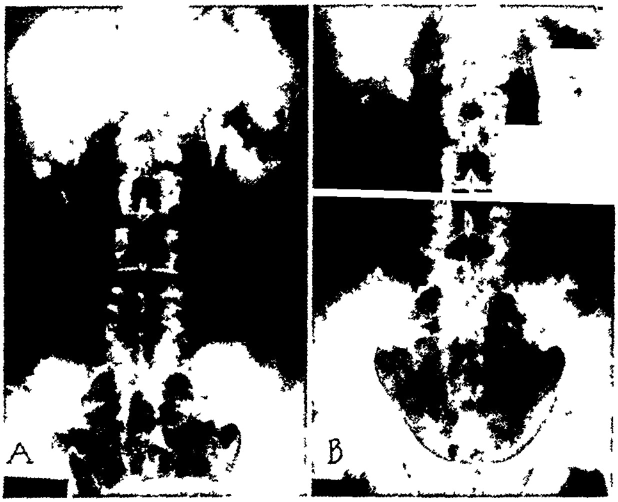

FIG. 3 Case 5 *A*, preoperative excretory urogram. Note complete duplication of right ureter *B*, excretory urogram 5 months postoperative Note dilatation of lower pelvis on right

patient was continent. Right pyelonephritis occurred 5 months postoperatively. A 5 months postoperative urogram revealed dilatation of the lower pelvis of the right kidney (fig. 3, *B*). At cystoscopy of the cecal bladder 6 months postoperatively we were unable to catheterize the ureters. The cecal bladder was explored transperitoneally February 9, 1953 because of the lower right ureteral obstruction. The new bladder was opened through a longitudinal band. The orifice from the right lower pelvis could not be located until the inferior surface of the bladder had been freed up and a band severed, which seemed to be kinking the intramural portion of this ureter. It would then admit an F6 ureteral catheter. Meatotomy of this ureter was performed with scissors after which an F10 ureteral catheter passed up easily (fig. 4). No chemical imbalance occurred at any time. Revision of the moderately strictured skin about the ileostomy was done under local infiltration anesthesia on April 22, 1953. The patient has been well and working since then.

The report of an interesting case of eosinophilic granuloma of the bladder follows:

Case 6. Mr. R. G., aged 54, No. 545921, complained bitterly of longstanding urgency, nocturia and lower abdominal pain. Previous surgery included left orchiectomy, postgonococcal, 1920, gastro-enterostomy 1924, transurethral prostatectomy 1934, 1950 and 1951, diaphragmatic hernia repair 1949, myelogram in 1950, all elsewhere. Preoperative excretory urograms revealed a normal upper urinary tract. Cystoscopy revealed a contracted injected bladder, biopsies were negative for tumor. An ileocecal bladder was made on April 24, 1952. Retrograde cystogram of this bladder 3 months postoperatively revealed no reflux. Excretory urograms 8 months postoperatively showed a normal upper urinary tract. Bladder capacity was 350 cc. Cystectomy was done February 17, 1953 because of continued vesical pain. The patient is continent. Blood chemistries have remained normal. The bladder was completely infiltrated by eosino-

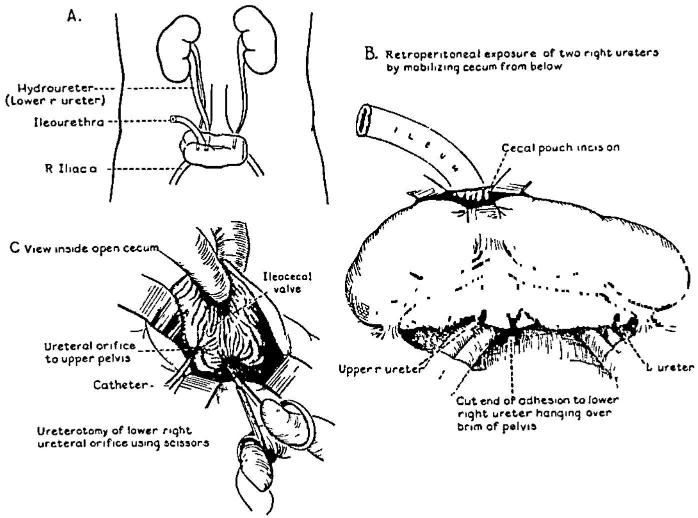
A.
Hydroureter
(Lower r ureter)
Ileourethra
R Iliaca
B. Retroperitoneal exposure of two right ureters by mobilizing cecum from below
Cecal pouch incision
Upper r ureter
L ureter
Cut end of adhesion to lower right ureter hanging over brim of pelvis
C View inside open cecum
Ileocecal valve
Ureteral orifice to upper pelvis
Catheter
Ureterotomy of lower right ureteral orifice using scissors

FIG 4. Case 5. *A*, diagrammatic sketch showing crossing of right ureters. *B*, view of inferior surface of cecal bladder, with retroperitoneal exposure of ureters. *C*, ureteral meatotomy with scissors, through opened cecum.

philes. Circulating eosinophiles were normal. Although the patient improved after cystectomy, he was much more comfortable after cortisone therapy and was able to return to work.

DISCUSSION

Continence. No patient has chosen or needed to wear a bag. The paraplegic, hydrocephalic 10 year old boy with exstrophy of the bladder was never continent or co-operative. For a week after surgery, a catheter is left in the bladder. Then a catheter is passed into the bladder every three or four hours. Considerable mucus is encountered in some patients, little in others. Most bladders hold between 320 and 500 cc. The colon segment has been 7 to 8 inches in length, ileum 4 to 5 inches in length. The ileal segment is cut off flush with the skin which is covered with a piece of gauze placed inside of a small plastic ice box jar cover. Continence becomes increasingly better as the patient becomes more ambulatory and the skin around the ileal opening contracts. This sometimes takes two to three months. Patients use a soft F18 catheter, not sterilized, but washed frequently. One patient catheterizes himself 3 times a day. One patient spills some with excitement when the bladder is full. Most empty the bladder every 3½ to 4 hours. The exception to this was the man with the eosinophilic granuloma who, until his bladder was removed at a second operation, was incontinent after 2 hours. However, he drank immense amounts of water and usually obtained 300 cc. Now he is continent up to 3½ hours. Several patients have had diminished bladder capacity accompanying periods of bowel upset.

Peck and Newland[5] have reported that three of their patients obtained continent ileocecal bladders. Santander of Venezuela[6] has reported obtaining continence in a 15 year old girl who had an obstetrical vesicovaginal, rectal fistula. Capides[7] states that of four patients subjected to the procedure, all were incontinent. Schmitz[8] reports two continent patients. Wenger[9] reported a continent patient. We bring the ileum out through a right sided stab wound almost on a level with the umbilicus midway between that landmark and the anterior superior spine of the ilium.

Pyelonephritis. Cultures of the cecal bladder urine, at varying intervals after surgery, have shown most of the common bacteria. In spite of this, pyelonephritis has occurred in only four patients, being transient in two, terminal in one and corrected apparently in case 5 by freeing an extrinsic band and ureteral meatotomy.

Chemical imbalance. In one patient who had many operations for postoperative intestinal obstruction, severe chemical imbalance developed after a jejunotransverse colon anastomosis with several feet of small bowel being left as a blind loop. He had severe diarrhea and chemical imbalance following this operation.

The aforementioned case was the only patient who required limitation of diet. One patient with mild hyperchloremic acidosis (female) has been controlled with one teaspoonful of baking soda thrice a day. All other patients have had normal nonprotein nitrogen, blood chloride and CO_2 combining power values after leaving the hospital.

Kinking and stricture of ileum. Two patients have required postoperative shortening of the ileum to eliminate kinking, a simple operation. Two needed minor revision of the strictured skin about the ileum.

Stricture and kinking of the ureters. Kinking of the ureter just above its entrance into the cecum occurred in one patient after re-implantation of the only ureter present. Kinking at the intramural portion of the transplant with slight stricture of the meatus occurred in the middle one of three ureters in one patient. This was due to an extrinsic adhesion. No ureteral strictures have been noted in our available postmortem specimens.

Reflux up the ureters. Retrograde cystograms have been done on many of the patients and in only one was any regurgitation shown. Postmortem reflux was described in one of our patients by Creevy.[3]

Calculi in bladder. Small single or multiple calculi have been found at postmortem examination in 2 patients, 18 months and 21 months after surgery. In one other patient, Case 2, the urograms suggested small calculi 19 months postoperatively, but cystoscopy failed to reveal them.

Cystoscopy and catheterization of the ureters. Cystoscopy and panendoscopy

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have been done one or more times in the majority of our patients This procedure usually causes bladder spasm in the conscious patient Because the ileum is led off the top of the segment, the ureteral orifices are somewhat behind the ileocecal valve in a retrograde fashion This makes the approach to the ureteral orifices somewhat awkward if not difficult If the ileum were placed lower, a more direct approach would be provided for the entrance of the cystoscope, effecting a better alignment for catheterizing the ureters This arrangement, however, would probably reduce continence Perhaps a better instrument for retrograde ureteral catheterization would be helpful

SUMMARY AND CONCLUSIONS

Eighteen cases are described in which the ileocecal segment was used as a substitute bladder The youngest patient was 10 years of age, the eldest 74 years old Vermeulen and Cole[10] have done this operation for exstrophy of the bladder in a 6 year old boy who was known to be continent with normal blood chemistry values for 18 months The indication for the procedure was the necessity for urinary diversion in surgery for pelvic cancer in sixteen cases and in two benign cases, namely eosinophilic granuloma of the bladder and exstrophy of the bladder in a ten year old paraplegic boy

Palliation only was attempted in six of the cancer cases, with one postoperative death The other 5 patients were dead within two years Small stones had developed in the bladder in one case

Cure with radical pelvic surgery was attempted in ten cases, with three postoperative deaths One patient died an unrelated cardiac death within one year The other died 21 months postoperatively with severe chemical imbalance following several operations for intestinal obstruction A small calculus was found in the bladder Five patients, or 50 per cent in this group have survived from 26 to 10 months, and are active One, however, has a recurrence at 11 months They are satisfied with their substitute bladders Some find the bladder easier to care for than the colostomy No patient wears a bag One patient takes sodium bicarbonate for mild acidosis

In the benign group, one patient has a well functioning bladder after 13 months

The ileocecal bladder, as described above, is of definite value as a reservoir for the urine in cases of pelvic evisceration We are using it increasingly ı management of infiltrating bladder tumors

ADDENDUM

We have constructed this substitute bladder in 27 cases Hyperchlorem dosis has not developed in later cases, the mild acidosis reported in case disappeared, and the kidneys are normal on excretory urography

We wish to acknowledge our appreciation for the advice and assistance by Drs Norris Heckel, Harry Boysen and George Hass of the urologic, cologic and pathologic sections of the Presbyterian Hospital

104 S Michigan Ave , Chicago 3, Ill (J W M)

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OBSERVATIONS ON THE USE OF THE CECUM AS A SUBSTITUTE URINARY BLADDER

JAMES G. M. HARPER, MICHAEL H. BERMAN, ARTHUR D. HERTZBERG, FRED LERMAN AND HERBERT BRENDLER

From the Urology Service, Bronx Veterans Administration Hospital, Bronx, N. Y.

In recent years with the advances in techniques of pelvic surgery, considerable interest has directed toward devising satisfactory methods of urinary diversion. These can be classed as follows:

1) Cutaneous fistulas including pyelostomy, nephrostomy, and cutaneous ureterostomy.

2) Transplantation of ureters to a portion of the bowel left in continuity, most common of which is ureterosigmoidostomy.

3) Transplantation of ureters into a portion of bowel which has been isolated from the fecal stream.

The first two methods have been used extensively and their advantages and disadvantages are well known. The third method has yet to be evaluated.

The use of the isolated cecum as a urinary bladder with a segment of attached ileum as a urethra has been described by Gilchrist and Merricks et al.[1, 2] Our purpose is to report our experience with this method in 7 cases.

TECHNIQUE

The bowel is prepared for 3 days with antibiotics, catharsis and enemas.

Using a right rectus or a transverse lower abdominal incision, the cecum, ascending colon and hepatic flexure are mobilized. The colon is divided between clamps at or near the hepatic flexure. The proximal portion is closed.

The ileum is divided about 6 inches proximal to the ileocecal valve and its mesentery divided down to its root, care being taken to preserve the important ileocecal vessels. Bowel continuity is re-established with an end-to-end or an end-to-side ileocolostomy.

The cecal bladder is swung 90 degrees clockwise so that the distal end lies to the left. The ileal stump is brought out through a stab wound in the right lower quadrant.

The ureters are then transplanted to the posterior portion of the cecum after the latter has been positioned so that the new urethra takes as straight a course as possible to the abdominal wall. A modified Coffey I method has been used in making the anastomoses.

A 26F Foley catheter with 30 cc bag is inserted under digital control to assure adequate drainage of urine, mucus and debris.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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The pelvic surgery such as cystectomy, pelvic lymph node dissection, etc , is now carried out or may be deferred to a second stage

Constant drainage of the cecum is supplied for 1–2 weeks, after which intermittent catheterization is instituted or an indwelling catheter is inserted and clamped off for intervals

RESULTS

Seven cases have been selected for this method of urinary diversion Six of these had carcinoma of the bladder, and 1 had multiple urethral fistulas to rectum, perineum, scrotum and penis with a contracted bladder Two of the cases of carcinoma had diversion done for palliation only, 1 had a two stage operation, and the remaining 3 cases had a one stage procedure, including preparation of cecal bladder and radical cystectomy with pelvic lymph node dissection All cases save one had two normal ureters transplanted to the cecum One case was found to have a pyo hydro ureter which was brought to the skin

Two deaths have occurred in this series The first was due to a pulmonary embolus 9 days postoperatively The second was due to generalized peritonitis and occurred 20 days postoperatively In both of these cases urinary output was adequate and blood chemistries remained within normal limits Autopsy was performed only on the second case Peritonitis was believed to have been caused by contamination during surgery from the right pyo ureter which was not anastomosed to the cecum but brought out to the skin instead At autopsy the kidney and ureter associated with the cecum were grossly normal

Excretory urograms in the 5 patients who have survived more than one month since surgery have shown 5 minute clearance of dye with only slight dilatation of ureters and pelvis one month following surgery

Blood chemistries including blood urea nitrogen, CO_2 combining power, chlorides, potassium and sodium have in all cases remained within normal limits

Complications have been 1) pulmonary embolus, causing one death, 2) peritonitis, causing the other death, 3) fecal fistula which closed spontaneously, 4) posterior wall myocardial infarction in the case in which the patient underwent a one stage procedure This was treated successfully by bed rest and anticoagulants

The final method of urinary drainage has been determined largely by the patients themselves after trial on intermittent catheterization, or indwelling Foley catheter with intermittent evacuation of accumulated urine The latter method has been chosen because it is more convenient Patients are able to clamp off the Foley catheter for 2–3 hours without leakage or discomfort The use of a 1 per cent solution of sodium bicarbonate for irrigation helps to keep the catheter clear of mucus

Cecometrograms performed on 2 patients have shown abrupt rises of 20–30 mm Hg in intracecal pressure at increments (steady flow) of 50 cc followed each time with return to resting level Peaks of the pressure rises go steadily higher (30–35 mm Hg) until pain is experienced and leakage occurs, this at 550 cc in one patient Cecograms performed on 3 patients have shown no ureteral reflux Endoscopic observation on 2 patients was resultant in the finding of only one ureteral bud

Follow-up periods for the 5 patients living have been 6 months, 5 months, 4 months, 3 months and 1 month. There have been no complications such as pyelonephritis, azotemia or acidosis in any of the patients since leaving the hospital. The first patient was brought back into the hospital 3 months after his operation to have his ileal loop shortened to facilitate replacement of catheter.

DISCUSSION

Impetus for this study has been provided by the deficiencies of current methods of urinary diversion. Ureterosigmoid anastomoses have developed serious sequelae such as retrograde infection with pyelonephritis, reabsorption of electrolytes with hyperchloremic acidosis, stricture formation at the anastomosis site with obstruction and uremia, and urinary extravasation with peritonitis. Ureterocutaneous transplants have too frequently caused trouble because of sloughing of the distal segment of ureter and subsequent stricture formation. The necessity for the use of indwelling ureteral catheters has resulted in infection and stone formation.

The advantages of using the isolated cecum as a urinary bladder with a loop of ileum as urethra have been enumerated by Gilchrist as 1) lack of fecal contamination, 2) lack of reabsorption of electrolytes and 3) continence because of the competence of the ileocecal valve and the peristaltic activity of a segment of ileum.

In our experience this method, though involving more operating time than other current methods, has paid dividends in ease of later management and in lack of serious complications. We have seen no urinary blockage and no kidney infection. There has been no evidence of reabsorption of electrolytes.

It is our impression that the patient with this type of diversion is happier in its management than one with ureterocutaneous transplants. He has been free of rubber urine storage bags and has not been troubled with soiling and leakage.

SUMMARY

Seven cases in which the cecum has been used as a substitute urinary bladder have been reported and discussed.

It is believed that in the long term analysis this method may show a superiority to other current methods in preventing urinary sepsis, obstruction and severe electrolyte imbalance.

We wish to express our appreciation to Consultant Dr. Archie L. Dean for sponsoring this presentation.

5062 55th Place, San Diego 15, Calif. (*J.G.M.H.*)

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INTESTINOVESICAL FISTULA

GEORGE H EWELL

Department of Urology, Jackson Clinic, Madison, Wis

Intestinovesical fistula is a serious medical and surgical lesion which we are seeing with greater frequency From my experience as a urological consultant, and as a member of the surgical team in most of the cases that have come to operation in our clinic, I shall attempt in this paper to summarize some of the clinical data and the diagnostic and surgical problems presented by these patients

These fistulas may be congenital or traumatic in origin or secondary to inflammatory or neoplastic lesions primary in either the gastro intestinal tract or the bladder For practical purposes I shall limit the discussion to those due to malignancy of the large bowel and those secondary to diverticulitis of the The latter group accounts for approximately 50 per cent of the cases, an are curable by surgical and other types of procedures Physicians should bear in mind that any patient having episodes of diverticulitis is a po candidate for the development of a fistula

Intestinovesical fistulas may occur at any age, the majority occurring b the ages of 40 and 70 In this age group occurs most cases of diverticuli malignancy of the sigmoid and rectum They are approximately five more common in men than in women, probably due to the presence and p of the uterus and to the less frequent occurrence of diverticulitis in wome

During the past 5 years we have observed 9 cases The youngest was the oldest 72 years, 2 cases were in women, one case in a man was due to nancy of the sigmoid

PATHOLOGY

It is important to bear in mind that in those lesions which are secon diverticulitis, the inflammatory reaction in the pelvis is often so marke it is almost impossible at times for the surgeon to determine by palpatio the presence or absence of an associated malignancy The same is true even following periods of prolonged colostomy drainage

SYMPTOMATOLOGY

The symptomatology is variable There are symptoms referable to testinal lesion, and those referable to the urinary bladder A 63 year-ol (D B) (Jackson Clinic No 106–845) came to the clinic only because quency, terminal dysuria and hematuria of a few months' duration His disclosed attacks of left lower abdominal quadrant pain for over thirty He gave no history of passage of blood from the rectum Examinations r a carcinoma of the sigmoid occurring in an area of diverticulosis At cyst examination numerous biopsy specimens were removed from an edemato

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Read at annual meeting, American Urological Association, St Louis, Mo Ma in the bladder mucosa, and all were reported as negative for tumor cells. Following a period of colostomy drainage and at the time of the definitive surgery, biopsy specimens were taken from the bladder wall, from the serosal surface of the bowel and from an adjacent mesenteric lymph node, and again no tumor cells were found in these sections. The bowel lesion was resected. Approximately one year later frequency and hematuria developed. Cystoscopic examination revealed a neoplasm, sections of which showed it to be of an intestinal type. He was treated by transurethral resection and deep x-ray therapy. Obviously, there were tumor cells present in the bladder wall, not demonstrated in the biopsy specimens which we made. The lesion by direct extention ultimately perforated the bowel, producing a vesico-intestinal fistula.

My experience with this case and in other cases secondary to malignancy, where the bowel lesion is amenable to surgery, leads me to believe that from a urological standpoint, unless a wide segment of the bladder wall can be resected, then some form of diversion of the urinary stream should be done with total cystectomy.

In those cases due to diverticulitis, the symptoms are usually those of the diverticulitis itself. With these attacks there may be recurrent attacks of cystitis. However, the attacks of cystitis may be present or precede any symptoms referable to the intestinal tract. One of our patients had mild recurrent attacks of cystitis for three years. He then developed pneumaturia and there were no symptoms referable to the intestinal tract.

The symptomatology of diverticulitis itself may be extremely vague and confusing. This statement may be best illustrated by referring again to the history of the patient whom we thought had an impending intestinovesical fistula. This patient, a 62 year old man (J. C.) (J. C. No. 166–388) came to the Clinic on the thirty-sixth day of his illness. His chief complaints on admission were weakness, fatigue, anorexia, afternoon temperature, frequency, and nocturia. He had been essentially well until the onset of his illness which began with weakness, fatigue, anorexia, and distress in the lower abdomen. His urinary symptoms, which consisted only of frequency day and night, did not begin until approximately ten days following the onset of his illness. He had been treated with antibiotics and other medications for an extended period before coming to the Clinic.

His urine on admission was normal in all respects. Cystoscopic examination revealed findings suggesting pressure from an extravesical mass. Urologic examination, which included excretory urograms, was otherwise normal. A cystogram confirmed the cystoscopic evidence of extravesical pressure. Abdominal exploration revealed an area of diverticulitis attached to the urinary bladder and a carcinoma of the cecum. The lesion of the cecum was not attached to the bladder. This lesion had been suspected clinically, but for various reasons no attempt had been made to delineate it completely by x-ray examination.

Cases of intestinovesical fistula, postoperative in origin, are usually ushered in with vesical symptoms. Chills and fever frequently accompany almost all types. Pneumaturia and the passage of feces through the urethra are usually spoken of as pathognomonic of intestinovesical fistula. Certainly this is true of the passage of fecal matter. It does not, however, occur as often as pneumaturia. Pneumaturia is not pathognomonic of intestinovesical fistula, since it may be due to other causes. It may best be stated, that if a patient complains of pneumaturia, it should be considered to be due to an intestinovesical fistula until proved to be due to some other cause. The passage of urine through the rectum is another cardinal but rather uncommon symptom of intestinovesical fistula.

In a few cases, the history alone will be sufficient for diagnosis. We have found that cystoscopy and cystography are the most valuable aids in diagnosis. In many of the cases the opening may be visualized, and in a few cases an unsuspected fistulous opening in the bladder has been found at cystoscopy. Frequently, the opening in the bladder is not seen, being obscured by an ulcerated or granulomatous area. Probing of the area with a ureteral catheter should be done cautiously to avoid creation of a fistula. Bubbles of gas or fecal matter extruding into the bladder may be observed. A biopsy from the area in the bladder should be made but is not always conclusive as to the presence or absence of carcinoma.

Increasingly we are appreciating the cystogram as a valuable diagnostic adjunct. We do the cystogram with both air and a nonopaque medium. The defect in the contour of the bladder wall is best shown on the film made with the patient in an oblique position. The defect somewhat resembles that of an infiltrating neoplasm of the urinary bladder (fig. 1). Unless there is marked inflammatory reaction of the bladder wall or unless the intestinovesical fistula is due to carcinoma of the bowel extending through the bladder wall, a negative filling defect within the cavity of the bladder is not observed as in a primary neoplasm of the bladder. Stewart has recently advocated the use of the delayed cystogram in suspected cases. Considering the nature of the disease, it is apparent that such a procedure will be of extreme value.

I believe that some of these lesions can be prevented. I have urged my medical colleagues to refer for urological examination those cases of diverticulosis in which the patients, while under treatment, have an attack of diverticulitis and subsequently have vesical symptoms.

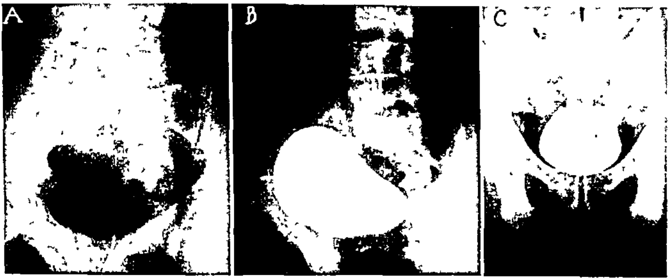

FIG 1 Note filling defect as if due to extravesical pressure, and suggestion of infiltration or inflammatory reaction in bladder wall

We have observed in one instance that neither the number, duration, nor severity of the attacks of diverticulitis appear to bear any definite relation to the development of an intestinovesical fistula, as shown by the case of a 35 year old man (R. F. M.) (J. C. No. 171–328) who came to the clinic in September of 1950. Since April 1948, he had experienced two or three mild attacks of left lower quadrant abdominal pain. X-ray examination had revealed diverticulosis. In August 1950, he had an attack of pain associated with fever and tenderness with some residual soreness which persisted for three or four weeks. No subsequent attacks occurred until August 1952, at which time some burning on urination developed. There was no frequency nor hematuria. His physician found pyuria and he received sulfonamide medication. The burning subsided in 3 days, after which time his physician found that he was running a low grade febrile reaction for which he was given penicillin and his temperature soon subsided to normal; the duration of the episode was approximately ten days. About this time, following the ingestion of some mineral oil, he noted oil globules in the urine.

This case is also interesting as it demonstrated the length of time required for the fistula to temporarily close spontaneously following the institution of colostomy drainage which was done in the transverse colon in this case. Forty-eight days following the institution of the colostomy, a petrolagar emulsion in water was introduced into the distal colostomy opening in order to soften and remove some masses of barium which still persisted in some of the diverticula. Oil globules soon appeared in the urine. Ten weeks was allowed to elapse before the involved segment of bowel was resected.

More attention should be paid to the patient's vesical function, and not too much significance attached to the absence of bacteria and cellular elements in the patient's catheterized urine. The combination of the sulfonamide drugs and the antibiotics which are so extensively used in the treatment of diverticulitis, may render a patient's urine sterile and relatively free from pus cells, even though an inflammatory process may be attached to the bladder wall. Such symptoms as frequency, nocturia, dysuria, and pain and discomfort in the suprapubic and bladder regions are prone to persist.

TREATMENT

No definite course of treatment can be outlined. Each case must be individualized. Most cases require a surgical procedure of some type. Carroll and others have reported curing cases of intestinovesical fistula by destroying the lining of the fistulous tract with a fulgurating electrode used through a cystoscope.

In the surgical management of these lesions the importance of a preliminary colostomy cannot be overemphasized. Morbidity, operative mortality, and the incidence of recurrence, are all definitely greater following a one-stage repair. Barnes and Hill, Ormond, Mayo and Blunt emphasize the importance of preliminary colostomy. Mayo and Blunt used colostomy in the majority of their 46 cases. They all point out that with the use of antibiotics a one-stage operation may be done more commonly than in the past.

SUMMARY

Intestinovesical fistula occurs commonly enough to warrant, on the part of all the physicians concerned in the management of these cases, a common knowledge of the diagnostic and surgical problems involved

Diverticulitis accounts for approximately 50 per cent of the cases of intestinovesical fistula In those cases in which diverticulitis is associated with urinary symptoms, it is suggested that consideration should be given to the prospect of the development of an intestinovesical fistula

Those cases due to diverticulitis are amenable to surgical treatment, and the number of recurrences is small In the surgical management of all types of these cases, a preliminary colostomy is extremely important, and in our experiences, when done in the transverse colon, simplifies the surgical approach to the fistula

The use of sulfonamides and antibiotics has made it possible to do more one-stage operations especially in those cases due to diverticulitis At the same time, in some cases these drugs may mask symptoms, with the development of a dormant abscess, so that medical treatment may be prolonged, when earlier surgical intervention would have prevented fistula formation

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CYTODYNAMIC PROPERTIES OF URINARY NEOPLASMS. IV. CULTIVATION IN VITRO OF TRANSITIONAL CELL CARCINOMA OF THE FEMALE URETHRA

R G BUNGE

From the Department of Urology, University Hospitals, State University of Iowa, Iowa City, Iowa

Previous papers have dealt with neoplasms of other portions of the urinary tract. The opportunity to study the in vitro characteristics of a carcinoma of the female urethra was a rare opportunity. While the female urethra may be involved by secondary neoplasms of the vagina or vulva, the occurrence of a neoplasm arising primarily in the female urethra is infrequent, although more frequent than in the male urethra.[1]

A 55 year old white woman appeared at the clinic, stating that 7 months previously she had noticed the onset of considerable bladder irritation. One month following the onset of these symptoms, a diagnosis of carcinoma of the urethra was made and a partial transurethral resection of the tumor was performed. Four months later another resection was done and this did not seem to control the tumor. On panendoscopic examination the entire urethra, except the meatal portion, was filled with a papillary growth which bled very easily on manipulation. The bladder was free of any visible neoplastic change and intravenous urograms were normal. At the time of operation several pieces were obtained with the resectoscope for incorporation in tissue culture.

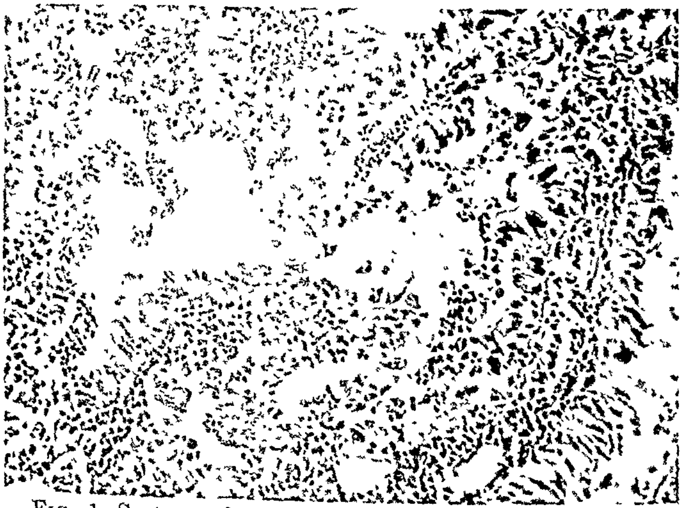

FIG. 1. Section of original neoplasm (H and E stain)

METHOD

Tissue removed from the urethra (fig. 1), with the resectoscope, was cut into small fragments approximately 1 mm. square, and washed for 20 minutes in three consecutive changes of Simm's ultrafiltrate, containing 100 units of penicillin.

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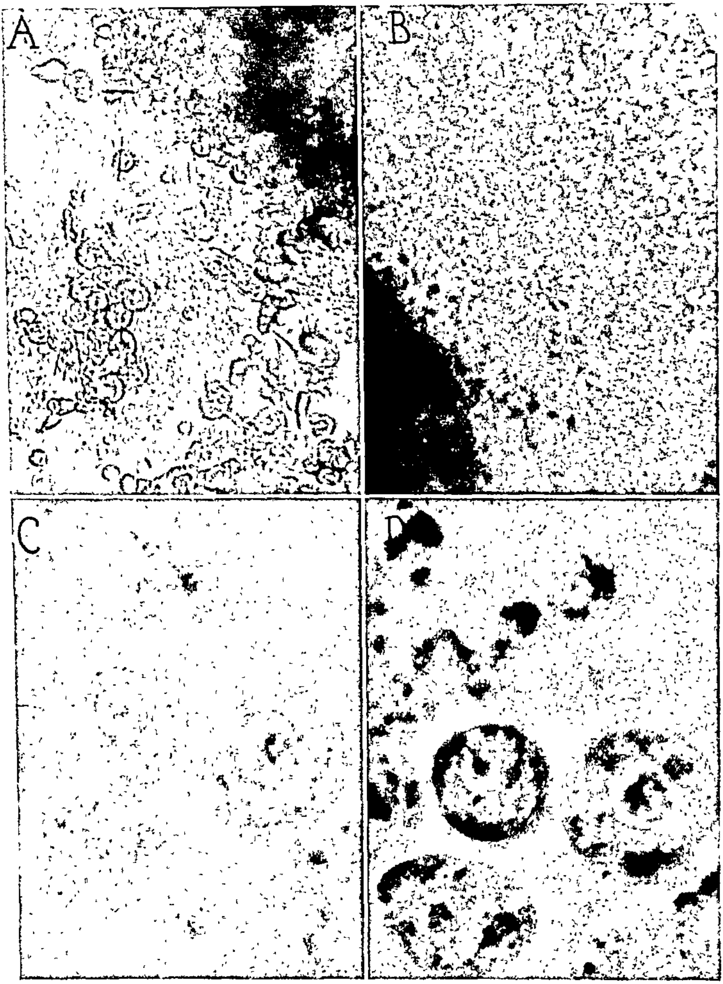

FIG. 2. *A*, culture at end of 24 hours. (× 125) *B*, culture at end of 1 week. (× 125) *C*, group of cells from 9 day old culture at moment of treatment with podophyllin, 1 mg. per liter. Phase optics. (× 1800) *D*, same cells 22 days later. Phase optics. (× 1800)

The fragments were then mounted on flying coverslips in chicken plasma and one drop of medium, consisting of 4.5 parts of balance-salt solution, 4.5 parts of ascitic fluid (obtained from a patient with carcinoma of the prostate), and one part of 50 per cent chick embryo extract, was added. Each ml. of balance-salt solution contained 10 units of penicillin. The cultures were then inverted over well-slides, sealed, and incubated at 37C. Refeeding of the cultures was carried out every third day.

OBSERVATIONS

During the first 24 hours some out-wandering cells were seen, the edges of the explant remained clear, and the cells appeared viable (fig. 2, A). Within 48 hours there were numerous out-sproutings of epithelial cells, and by 96 hours (fig. 2, B) luxuriant growth of epithelial cells was observed in 80 per cent of the cultures. Contrary to previous observations in tissue culture of transitional cell carcinoma of the bladder and ureter, no "tadpole" cells were seen in our cultures of this carcinoma.

Fibrocytic growth was absent and the cultures were kept under observation for two weeks and then discarded. Three cultures were treated with podophyllin, 1 mg. per liter, and no adverse effect was noted on the cells. Podophyllin was prepared by precipitation from a 95 per cent ethyl alcohol solution in 10 per cent gum acacia and diluted in balanced-salt solution to a concentration of 1 mg. per liter.[2]

In one instance a nine day old culture was removed with a small portion of its medium, treated with podophyllin, sealed on a microscope slide with vaseline, and kept under observation for 22 days at room temperature with phase optics. No detectable morphologic alteration occurred in the cells (fig. 2, *C* and *D*).

DISCUSSION

The patient was treated with bladder instillations of 2 per cent podophyllin in mineral oil suspension every other day for two weeks and panendoscopically, little effect could be seen on the tumor. This confirmed the observations in the tissue culture laboratory.

Some papillary bladder tumors in tissue culture are sensitive to podophyllin in concentrations used in these observations;[3] the failure of this urethral papillary tumor to respond suggests a biological difference.

The cultures sealed with vaseline and kept under continuous observation for 22 days were not refed and it was, indeed, surprising to see the lack of morphologic deterioration of the cells. Among other things this suggests a biological hardiness of these particular types of neoplastic cells arising from transitional epithelium. Perhaps the so-called "seeding" of these tumors can in some degree be explained on their ability to survive under adverse conditions.

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PEYRONIE'S DISEASE A NEW APPROACH

GERALD H TEASLEY

Peyronie's disease has long been a disturbing problem to urologists No treatment has been recommended that is outstandingly satisfactory It is a disease seen infrequently It is not incapacitating, nor does it shorten life However, it is definitely irritating to the individual who has it and is a major problem to the person concerned No effort will be made in this paper to outline the etiological background of this disease, to discuss its pathology, nor indicate the forms of treatment advocated to this date It is my purpose to bring to you the results of treatment by a method first reported to the intercity urologic group at Dallas in June 1952 Through the help of members of that group and others, I am able to report more cases than would have been possible otherwise Since my arrival in St Louis, I have been told that the subject was discussed at one of the Section meetings in March 1953, but no references are to be found in the literature to my knowledge, which can be listed for this type of treatment Personal communications from other physicians who have used these injections have been the main source of outside information I would herewith like to express my appreciation to Dr Reed M Nesbit and Dr William C Baum for their courtesy and co operation in the use of injections for 12 patients, Dr Dolphus Compere, Fort Worth, Dr Jack Crow, Abilene, Texas, Dr A Keller Doss, Fort Worth, and Dr Ken Mooney, of Dallas Through their efforts I am able to report the use of cortisone in the treatment of Peyronie's disease on 24 patients

It is known that cortisone has a definite effect on connective tissue Large doses delay fibroplasia, and it has the capacity of inhibiting the genesis of fibrals, as demonstrated in cultures of fibroblasts After prolonged application on the skin there is a reduction in the number of fibroblasts present, and residual cells are often shrunken Elastic fibers are not so affected The drug also seems to exert an inhibitory effect on the development of pericardial, pleural, and peritoneal adhesions produced experimentally in animals Patients with Dupuytren's contraction have shown increased mobility following its use It has been recommended for the treatment of interstitial cystitis and urethral stricture in the field of Urology

The question of its use in Peyronie's disease was introduced after the surgical associate in our group, Dr Louis P Good, had shown me the results of injection for adhesions about a joint following trauma It occurred to me that the removal of fibrous connective tissue in this area might be duplicated in Peyronie's disease Accordingly, a patient was called whom I knew had this condition It was explained to him that this was an entirely new idea He had used tocopherols for several months without favorable results He was 65 years of age and had been unable to have intercourse for several months on account of poor erections He consented to try the suggested treatment and 25 mg of Cortone was injected directly into the placque on the dorsum of the penis Minor improvement was

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noted at the end of one week so they were continued for a total of six injections. The injections were stopped because the patient was able to have practically normal erection and intercourse, which had been impossible prior to that time. He has been seen at intervals for 8 months and reports no recurrence of his difficulty.

The second patient was referred because of discomfort during nocturnal erections and inability to have intercourse. After three injections he reported 25–30 per cent improvement, and after six injections approximately 75 per cent improvement. Intercourse was not so satisfactory as in previous years but was a definite possibility now, and the painful nocturnal erections no longer occurred. This man was 58 years of age. The third patient was a young man of 32 years. After the second injection he was able to have intercourse without difficulty. In his particular case there was a fibrous band completely around the corpora. This had disappeared at the completion of the injections. He was very happy over the results. The fourth person had a small pea-sized nodule between the corpora and dorsum of the phallus. It has shown a definite regression, and the curvature has been definitely decreased. This man was 46 years of age. A definite decrease has been noticed in the size of the placque, and the curvature has changed on the side where the placque is smaller. Observation on this patient is not complete, but it is believed that he will continue to improve since indications are now that the placque is disappearing.

Dr. William C. Baum, Section of Urology, University of Michigan, has treated 12 cases. In his first letter, after treating four individuals, he stated that there had been a spectacular resolution of the placque on the dorsum of the penis in one case, with relief of the curvature and pain. In two others there was partial resolution, and the third had not been seen. In a second letter he states, "First of all we can say that in no case was the administration of the drug a complete failure. Likewise, in no case can we say that there was complete resolution of the disease process as a result of the administration of the agent. In 2 cases there was complete disappearance of what appeared to be a large placque on the dorsal surface of the penis in the midline only to have it recur within a month of the conclusion of the treatment to a lesser degree, to be sure, but definite on palpation with return of the abnormal curvature on erection. In all cases there was an initial reduction in the size of the lesion on injection, all had definite relief as far as diminution in the pain associated with intercourse and in the majority of cases this pain has disapperared for good as a result of the therapy but again in none of the cases was there complete disappearance in the abnormal curvature of the penis."

Dr. Jack Crow reports treatment of three cases with excellent results.

Dr. Dolphus Compere reports 2 cases with improvement in the curvature and decrease in the rigidity of the placque.

Dr. Keller Doss writes that he had personally treated 1 case. The patient stated that he was better, intercourse was easier, and he wanted more treatments if necessary. Doctor Doss could not see any clinical change on examination.

Dr. Ken Mooney treated 2 patients, one aged 63 and one 49, both of whom thought they had definitely improved and asked for a second course of five injections.

This means a total of 24 cases treated.

The treatment used is as follows: The skin is cleansed with soap and water and some disinfectant. Then, using ½ per cent procaine solution, the skin and subcutaneous tissue, down to and around the placque, are infiltrated to control pain of injection. An ordinary hypodermic syringe and needle are used for this. After the local anesthetic has had time to take effect, the syringe and needle are discarded and a Luer Lok type of syringe, with an 18–20 gauge needle, is next used. A solution of 25 mg. of Cortone, dissolved in normal saline containing ¼ per cent of procaine crystals, is prepared. This will make approximately 1¼ to 1½ cc. This is injected directly into the placque. It is quite difficult to inject, and unless a Luer Lok syringe is used the needle will be blown off the syringe. Injections are repeated at intervals of one week. Personally, I used 6 injections before complete disappearance of the placque. The local internists tell me that there is no complication to be expected using such a small dosage; however, I believe that an internist should be consulted about the use of Cortone in any case where some condition exists which might contraindicate the use of this preparation. Figure 1 indicates the simplicity of preparing the injection and all the instruments required.

It has been my experience that variable results from each injection vary directly with the difficulty with injecting the solution. When the needle can be felt to scrape against the hard placque and definitely enter its substance so that injection is particularly difficult, the results within a week's time have been decidedly better. Injection about the placque will, in my opinion, produce no complete resolution of the fibrous process. There is very little pain connected with the procedure, and moderate soreness between injections has been the only

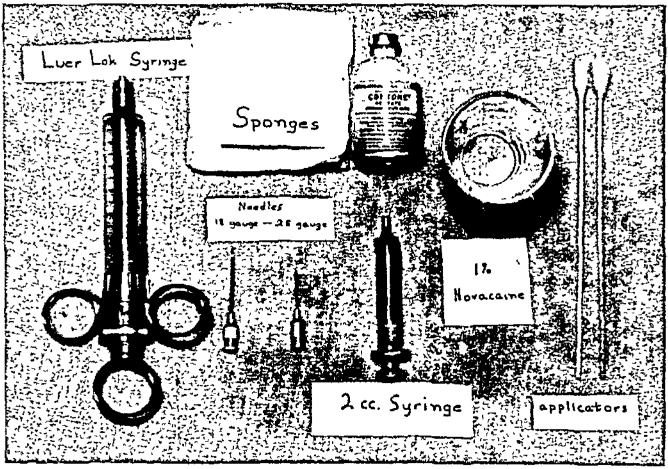

FIG. 1

complaint. Occasionally there is a mild subcutaneous hemorrhage, which has been of no significance. Due to the force required for injection when the needle is in the proper place, it is essential that a Luer-Lok syringe with the metal finger guards be used. Otherwise it is impossible to inject the solution.

SUMMARY AND CONCLUSIONS

Peyronie's disease is a fairly uncommon urologic problem which does not shorten life, is not a serious disease, but is of extreme importance to the person concerned.

The treatment of this condition has been generally unsatisfactory.

A new approach to the care of these patients is offered. It combines an office procedure with simplicity and comparative ease of administration.

There is no reason to assume that any deleterious systemic effect will arise from the use of such small dosage.

In the event of return of symptoms, there is no reason to withhold repeated series of treatment.

I have made it a practice to ask the following question of the four patients treated: If you had known beforehand the results you have obtained now, would you repeat the treatment? In each instance the answer was "yes". This, in my opinion, is the best recommendation I can give for this proposed treatment of Peyronie's disease.

401 E. Fifth St., Texarkana, Arkansas-Texas

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ROUTINE USE OF ANTIBIOTICS IN TRANSURETHRAL PROSTATIC RESECTION· A CLINICAL INVESTIGATION

C D CREEVY AND M J FEENEY

From the Division of Urology in the Department of Surgery in the Medical School, Minneapolis, Minn

Prior to the advent of the antibiotics, infection was undoubtedly the most serious complication of operations upon the prostate In 1905 Whiteside estimated the mortality of prostatectomy at 20 per cent In 1915 Tenney and Chase reviewed 229 deaths after prostatectomy, judging by their figures, infection must have played an important role in 65 per cent of the fatalities In 1923, Young's mortality was 3 2 per cent in 1049 consecutive perineal prostatectomies and, in 1936, Hunt and Walters estimated theirs at 5 4 per cent in 1000 consecutive suprapubic operations These figures do not allow for deaths occurring during preoperative "preparation" with the inlying catheter or cystostomy, a fact which Alcock emphasized in his early discussions of the transurethral operation As late as 1937 Rolnick and Riskind estimated the risk of suprapubic cystostomy at 28 6 per cent, mostly from infection The picture has changed remarkably with the development of potent antibiotics, so that it is now quite unusual to lose a patient with prostatism before removal of the gland

The mortality of enucleation has never declined much below that of Young and of Hunt and Walters (4 3 per cent in 2049 cases) in large series Two thousand seven hundred and sixty cases done by the perineal, suprapubic, and retropubic routes were collected from the literature between 1945 and 1950, the surgical mortality was 5 3 per cent (Creevy)

On the other hand, transurethral resection has become much safer since Alcock's report in 1932 of 6 5 per cent of fatalities in his first 400 cases It was possible in 1951 to collect from the literature and from personal experience 16,092 cases with a mortality of 1 30 per cent (Creevy) While much of this improvement has followed the use of antibiotics, there are no systematic studies of their effects upon morbidity and mortality

The causes of infection after urethral instrumentation and prostatectomy are well known Maresch and Chiari recognized the presence of pathogenic bacteria in the normal urethra, having cultured staphylococci, streptococci, diplococci, E coli, and B proteus in the absence of disease or previous instrumentation One can only guess how often the prostate harbors bacteria without symptoms The frequency of urethral discharge from inlying catheters requires no documentation Creevy has shown that pathogenic organisms may be recovered from used bed linen not grossly soiled, since an inlying catheter necessarily comes in contact with it and often with the anus, this must be an important route of infection

The role of urethral instrumentation in inciting infection is well understood

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Trauma makes a culture medium of the injured tissues and, by damaging vessels, permits bacteria to enter the blood stream. Clado and Halle in 1887 obtained positive blood cultures during urethral chills as did Crabtree in 1916. Scott later found bacteremia in 62 per cent of patients with fever after urethral instrumentation or operations upon the urinary tract. Barrington and Wright reported similar findings in 56 per cent as did Powers in 10 per cent after urethral dilatation. Thompson and Biorn found transitory bacteremia after 12 per cent of 106 transurethral resections. Moreover, prostatic operations leave devitalized tissue which encourages growth of organisms already present. McLaughlin attributed 6 of 16 deaths after transurethral resection to septicemia. Finn and Kane have reported 4 cases of enterococcal endocarditis in patients with a history of urethral instrumentation, three of them with known pre-existing cardiac valvular lesions.

The importance of infection following transurethral resection has been widely emphasized. Alcock feared it when the operation was first applied to larger glands; Chetwood and Orr felt the same both from personal experience and from answers to questionnaires sent to resectionists. Kretschmer observed fevers above 101F in 26 per cent and above 103F in 9.6 per cent of his patients; Davis found chills and fever after 6 per cent of his operations. Abeshouse alleges that infections are more troublesome after endoscopic than after open prostatic operations, although most resectionists will disagree. The potential seriousness of the problem is indicated by Meneely's report of two and Merritt's of 8 cases of bacterial endocarditis after endoscopic resection of the prostate in patients with old healed valvular defects.

Promising results have been reported from routine antibacterial therapy in connection with transurethral resection. Strom and Thompson thought that the use of sulfathiazole minimized postoperative fever; Prince found the urine sterile at the time of dismissal in 17 of 36 patients treated with sulfadiazine and penicillin, and Carroll had nine with sterile postoperative urine after aureomycin. One must admit, however, that failure of organisms to grow out of urine saturated with antibiotics does not mean that they are dead.

There is another factor in transurethral resection which may lead to bacteremia and which may serve as a test object in assessing the effectiveness of antibiotics: the washing of bacteria from the bladder or prostate into large veins opened by the surgeon. During a study of the hemolysis which often accompanies irrigation with distilled water during this operation, it was found that the substitution of 4 per cent glucose for distilled water prevented hemolysis and led to a rise in the blood sugar. Glucose must therefore enter the circulation, since the vesical mucosa ordinarily is incapable of absorption. These observations led to the performance of blood cultures at the conclusion of resection. They were positive in 43 of 94 consecutive patients who received no antibiotics. Thereafter the urine was cultured before operation and the blood just afterward; the urine was again cultured upon removal of the catheter in patients given a variety of antibiotics. Eleven antibiotics or combinations thereof have been tested in this fashion. It is our purpose to study their effects upon postoperative febrile

TABLE 1 *Frequency of postoperative infections in 888 cases*

COMPLICATION	NUMBER	PER CENT
Fever 101–102.8F	302	34.0
Fever 103F or higher	78	8.7
Funiculitis	17	1.9
Pyelonephritis	13	1.4
Prostatitis, vesiculitis	13	1.4
Epididymitis	12	1.3
Thrombophlebitis	8	0.9
Periurethritis	6	0.6
Pneumonia	5	0.5
Total	454	

reactions, *bacteremia, and mortality. The relationship between the organisms* of the urine and those of the blood is also considered.

Table 1 summarizes the occurrence of infections of various types in our whole study of 888 cases.

Many patients had more than one type of infection. Fifty-one per cent had some evidence of infection, assuming that it produced all fevers, although the vast majority of these were mild. In order to simplify the tabulations and because we are not here interested in the various types of infections, all of those listed separately in table 1 are combined in table 2 as "All Other Infections."

The series vary in length mainly because a regimen was abandoned either when sufficient data concerning a drug had accumulated, when it became

TABLE 2 *Influence of antibacterial agents upon postoperative infections*

SERIES	TOTAL CASES	FEVER TO 102.8F	FEVER 103F OR MORE	ALL OTHER INFECTIONS	MORTALITY
I Control	94	32.0%	9.0%	9.0%	1.0%
Group A					
II Penicillin	129	36.4	15.5	10.1	2.3
III Penicillin-sulfadiazine	98	40.9	20.1	9.2	3.1
IV Penicillin, streptomycin	75	45.4	8.0	12.0	2.7
V Penicillin-streptomycin-sulfadiazine	30	23.3	13.3	13.3	3.3
VI Triple sulfa	23	47.8	13.1	8.7	0
Total	355		Average		2.52
Group B					
VII Gantrisin	94	29.0	6.5	5.3	0
VIII Chloramphenicol	99	34.3	5.5	6.6	0
IX Aureomycin	121	25.6	1.6	4.1	0.8
X Terramycin	77	23.4	2.6	11.7	0
XI Chlor and Gantrisin	48	31.2	2.0	6.0	0
Total	439		Average		0.20

evident that it did not influence the incidence of bacteremia, or when it caused too many reactions. Table 2 shows that the frequency of high fevers was reduced only by the drugs in Group B, and especially by aureomycin, the superiority of which is also seen in "all other infections." There is also a striking difference in mortality between the two groups. It was felt that the influence of these drugs upon the bacteremia observed at the end of transurethral resection in 45.7 per cent of the controls would indicate their potential value. Table 3 summarizes this study.

This explains the reduced incidence of high fevers and complicating infections with the newer antibiotics in transurethral resection: they prevent, much better than the older ones, the survival in the blood stream of the causative pathogens. They doubtless reduce bacterial growth in the tissues and thus the surgical mortality; table 2 supports this view. The proportion of positive cultures was much higher in every group than was reported by Biorn and Thompson, a fact which we attribute to our effort to leave only the surgical capsule. This invariably opens large prostatic and periprostatic veins, and gives resident bacteria free access to the circulation.

THE FLORA OF THE URINE IN RELATION TO THAT OF THE BLOOD

The urine was cultured before and the blood just after operation in 356 cases. The urine was sterile in 102 of these, while the blood culture was positive in but 11, or 10.8 per cent. The urine was infected in 254 before operation. In this group the blood was infected in 146 or 57.5 per cent, suggesting that the urinary bacteria produce the positive blood cultures. The fact that, when both blood and urine contained organisms (146 cases), the same species was found in both 106 or 72.6 per cent confirms this view. Two sources of error make these conclusions tentative: the urine may have become infected between the time of culture and that of operation; and bacteria from the prostate may have produced a positive blood culture when the urine itself was sterile. It seemed unwise to massage the prostate preoperatively in the presence of urinary retention to clarify this point.

THE EFFECT OF ANTIBIOTICS UPON THE BACTERIAL FLORA OF THE BLOOD

It was soon observed that this was altered when antibiotics were used. Those in Group A produced relatively few changes when compared to the controls, but those in Group B not only reduced the frequency of positive blood cultures (table 3) but also changed its flora considerably. Most conspicuous was the increase in the frequency of Pseudomonas aeruginosa after chloramphenicol, Gantrisin, or both. While Terramycin and chloramphenicol were least effective against B. proteus, it grew out more often in Group B than in the controls or in Group A. Although the series are not large enough to permit final conclusions, the results are so consistent as to be strongly suggestive.

The less frequent appearance of Proteus and Pseudomonas in the blood in Group A may be due to the greater potency of these drugs against them, or to their lack of effect against other organisms, which then overgrew the Proteus and Pseudomonas in the cultures; those in Group B may have killed the other bac-

TABLE 3 *Antibiotics and bacteremia*

ANTIBIOTIC	NUMBER CASES	POSITIVE CULTURES	
		Number	Per cent
None	94	43	45.7
Group A	325	145	44.6
Group B			
Gantrisin	94	22	23.4
Chloramphenicol	96	30	31.2
Aureomycin	121	21	17.4
Terramycin	77	16	20.8
Chloramphenicol, Gantrisin	41	9	22.0
	429	98	22.9 (av.)

teria, thus permitting Proteus and Pseudomonas to grow. The latter hypothesis seems more reasonable when the clinical effectiveness of the wide spectrum agents is considered.

DISCUSSION

What is accomplished by routine use of antibiotics in connection with transurethral resection? While they may be unnecessary when the urine is sterile, one must remember that the prostate may harbor virulent organisms despite a sterile urine. Furthermore, catheterization after culture but before operation may infect a previously sterile urine. Table 2 shows that the incidence of fevers below 103F is not influenced by any antibiotics, thus suggesting their origin from absorption of toxins from burned tissues or from other nonbacterial factors. Fevers of 103F or over, on the other hand, are greatly reduced in frequency, and there is a definite reduction in the incidence of the "other infections" with antibiotics of Group B; such fevers occurred in 9 per cent of the controls, in 15.4 per cent of those in Group A, and in but 3.6 per cent of those in Group B. The best showing was made by Aureomycin with but 1.6 per cent of fevers above 103F. Similarly but less strikingly, "other infections" were seen in 9 per cent of the controls, in 16 per cent of Group A and in 6.5 per cent of Group B. Here also Aureomycin appears most effective. These facts bear out our clinical impression that convalescence in general has been much smoother since the antibiotics of Group B have been under investigation. It is gratifying that the overall surgical mortality for the whole group of 888 patients was but 1.24 per cent despite the fact that most were operated upon by residents learning the operation, and that there were many debilitated patients in the group. Also noteworthy is the difference in mortality (table 2) between Group A—2.52 per cent, and Group B—0.20 per cent. The series appear to be large enough to make this difference significant.

The dangers of bacteremia with virulent organisms are well known. The occurrence of subacute bacterial endocarditis after transurethral resection in patients with old cardiac valvular lesions (Meneely and Merritt) has already been mentioned. Waisbren has recently observed circulatory collapse in 15 instances of bacteremia with Gram negative rods. The cause of this circulatory collapse is not clear, but the kidneys may be damaged therein both by bacterial toxins and by renal ischemia. Van Slyke et al. have observed virtual cessation of glomerular circulation during severe hypotension. This slowing of the renal circulation in the presence of virulent bacteria may serve to hold the organisms in the kidneys. Such a renal ischemia may be aggravated during transurethral resection by a mechanism described by Corcoran and Page, who found transitory azotemia in dogs after severe bleeding with blood pressure maintained at normal levels by the simultaneous administration of fluids. They attributed it to intense renal vasoconstriction, compensatory in character, associated with the loss of blood even in the absence of hypotension. Since considerable quantities of blood may be lost during transurethral resection and since anesthesia may also lower blood pressure, it is apparent that even a mild bacteremia may injure ischemic kidneys, especially those diseased beforehand.

As previously noted, sepsis has always been one of the troublesome complications of prostatic operations. It has been blamed by Laughlin for 6 deaths in 535 and by Thompson for 6 in 1200 transurethral resections. Moreover, 8 of the 11 deaths in our 888 cases were due directly to sepsis. While our overall mortality was only 1.24 per cent, it would have been but 0.33 if deaths from sepsis could have been prevented. It seems therefore that an endeavor to eliminate this factor is well worth while, even though it involves the use of expensive antibiotics which may sometimes have unpleasant side effects. This is substantiated by the difference in surgical mortality between the two groups.

COMMENTS UPON VARIOUS ANTIBIOTICS

Penicillin is ineffective against infections due to the Gram negative rods predominant in our cases. It is best used for Gram positive cocci and, in combination with a wide spectrum agent such as Aureomycin, in fulminating infections while the offending organism is being identified. The usual dose was 500,000 units of crystalline penicillin G intramuscularly twice a day. Reactions were infrequent and mild.

Sulfadiazine was not used alone but was given with penicillin until it was evident from 98 cases (table 2) that it was ineffective. The dose was 0.5 gm. 4 times daily.

Streptomycin, because of the rapidity with which bacterial resistance to it rises, was not used alone. Combined with penicillin it appeared to reduce the frequency of severe febrile reactions somewhat, but the combination was abandoned because of the nuisance to the patient of the repeated injections, particularly when newer drugs were found to be more effective. The addition of sulfadiazine to the combination of penicillin and streptomycin served merely to produce anorexia, low fevers, and an occasional rash. The dose of streptomycin was 0.25 gm. 2 to 4 times daily.

A triple sulfonamide caused so many annoying reactions that it was discarded. The dose was the same as that of sulfadiazine.

Gantrisin is the most effective agent thus far discussed, having reduced the frequency of high fevers and of "other infections" by about one half (table 2) It was discontinued in 5 per cent because of side effects, chiefly fevers, but produced no severe reactions (granulocytopenia has been reported) in a dose of one to two grams four times daily It did not reduce the frequency of B proteus in the blood cultures

Chloramphenicol reduced the incidence of severe febrile reactions and "other infections," and caused no serious toxic effects Used alone it has been relatively impotent against B proteus The urine from 75 patients treated with this drug before and after resection was cultured on the third postoperative day It was sterile in 32 (42 per cent) In the 43 infected urines B proteus was found in 37, a paracolon bacillus in 26, and Pseudomonas aeruginosa in 37 per cent Compared to Aureomycin, chloramphenicol reduced slightly the frequency of B proteus, was more potent against the paracolon bacillus, but resulted in a remarkable increase in infections with Pseudomonas aeruginosa, against which it appears to exert no effect Patients received 0 5 gm the night before and on the morning of operation, then 0 25 gm 4 times daily until the evening after removal of the catheter It may be that 0 5 gm 4 times daily would have been better

Chloramphenicol and Gantrisin were tried together in the hope of more effect against B proteus This study was dropped when the relationship between chloramphenicol and aplastic anemia was discovered and contains but 48 cases From these limited data (table 2) this combination prevented high fevers and "other infections" better than anything but Aureomycin, it also reduced the frequency of B proteus and paracolon bacilli in the postoperative blood cultures Further investigation is intended The dose was ½ gm of chloramphenicol and 2 grams of Gantrisin on the evening before and again on the morning of operation and four times daily thereafter until removal of the inlying catheter

Aureomycin was the most effective drug used It reduced the percentage of positive blood cultures from 15 7 per cent in the controls to 17 per cent, severe febrile reactions dropped to 1 6 and "other infections" to 4 1 per cent Particularly gratifying was the reduction in incidence of bacteremias with Aerobacter aerogenes from 8 per cent in the controls and 11 2 in Group A to 0 8 per cent Twelve per cent of the patients had some untoward reaction such as nausea, anorexia, or diarrhea, but rarely was it necessary to stop its use for these reasons In one case septicemia developed with B proteus while it was being used, and many had strains of Aureomycin resistant bacteria in the urine on the third postoperative day Forty four of 72 patients (61 per cent) had positive cultures at this time Of these, 44 per cent had B proteus, 54 per cent paracolon bacilli, and 2 per cent Pseudomonas

It is evident from these last two tabulations that Aureomycin is somewhat less potent against B proteus, much less effective against paracolon bacilli, and far more effective against Pseudomonas than is the combination of chloramphenicol and Gantrisin

It is interesting to speculate as to the much greater frequency (both absolute and relative) with which these organisms were found in the urine than in the blood when chloramphenicol or Aureomycin were used It may be a question of postoperative contamination of the catheters and then of the urine by the bacteria of the bowel. Aureomycin 0.5 gm. was given on the evening before and again on the morning of operation, after which 0.25 gm. was given every six hours until the evening following removal of the catheter.

Terramycin is generally regarded as very similar to Aureomycin, but in our hands it caused diarrhea so often that its use was abandoned, after a second batch had the same effect as the first. It is realized that others have found Aureomycin as bad as Terramycin in this regard.

THE TREATMENT OF SEVERE INFECTIONS

Prompt recognition of circulatory collapse due to bacteremia is essential to a safe recovery. It differs from surgical shock and from collapse due to cardiovascular disorders in that it appears with a severe chill and cyanosis. Oliguria and fever follow. The foot of the bed is at once elevated, oxygen is administered, the blood is cultured, and transfusion is begun. Vasoconstrictors such as neosynephrin and norepinephrine are used only in alarming and persistent hypotension.

The use of adrenal cortical extract or of cortisone has been advocated in surgical shock and in sudden circulatory collapse but there is as yet no evidence of its value. Kurland and Freedberg have shown that the pressor response to norepinephrine is increased by the preliminary administration of cortisone or ACTH, but Harrison has pointed out that the use of norepinephrine in the presence of an excess of cortical hormones may cause renal ischemia and anuria.

Pending result of the blood culture, 0.5 gm. of Aureomycin is given intravenously supplemented by 500,000 units of penicillin intramuscularly to secure as wide an antibacterial spectrum as possible. Subsequent selection of drug and dosage depends upon circumstances. If the offending organism proves to be B. proteus, the use of chloramphenicol and Gantrisin together is considered. The rare septicemias with Pseudomonas aeruginosa may call for polymixin B. Treatment with antibiotics is continued until the patient is able to urinate satisfactorily without the catheter.

The diligent application of these measures has certainly saved lives that would have been lost without them.

SUMMARY AND CONCLUSIONS

Positive cultures were obtained from the blood drawn at the conclusion of transurethral resection in 45.6 per cent of 94 patients in the absence of antibiotics.

The use of "wide spectrum" antibiotics (Aureomycin, Terramycin, chloramphenicol, Gantrisin) starting just before operation reduced the incidence of bacteremia remarkably.

Severe postoperative fevers and localized infections were also reduced in frequency, as was the surgical mortality (2.5 percent with earlier antibiotics to 0.2 per cent with the newer ones).

Aureomycin appeared to be the most effective agent used.

B. proteus and Pseudomonas aeruginosa are the most resistant organisms of those commonly encountered.

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INTRAPROSTATIC INJECTION OF RADIOACTIVE COLLOIDS. I. DISTRIBUTION AND EXCRETION FOLLOWING INJECTION IN THE DOG

JOHN A. D. COOPER,* GEORGE J. BULKLEY AND VINCENT J. O'CONOR

From the Departments of Biochemistry and Urology, Northwestern University Medical School, Chicago, Ill.

Interest in treatment of carcinoma of the prostate by radiation has been revived by the favorable report of Flocks and his coworkers† on the results obtained in patients who were injected intraprostatically with colloidal radiogold using a retropubic or perineal approach. Since studies on the distribution and excretion of the radiocolloid following injection into the prostate have not been reported, we have undertaken such studies in the dog. In addition, we have made comparisons of radioactive colloidal chromic phosphate and colloidal radiogold with regard to their excretion and distribution after intraprostatic injection. Because of the rapid expansion in this field, we believed that a preliminary report of the results of our studies would be interesting at this time.

MATERIALS AND METHODS

Colloidal chromic phosphate containing P^{32} and colloidal gold (Au^{198}) were obtained on allocation from the U. S. Atomic Energy Commission and purchased from Abbott Laboratories. The majority of particles of chromic phosphate were reported to be between 1 and 2 microns in diameter with some larger particles present from aggregation of the smaller particles. The suspension was stabilized in 2 per cent pectin. The colloidal gold particles were 0.002 to 0.007 microns in diameter and the suspension was stabilized with 5 per cent gelatin. The preparations were diluted behind lead shields to an activity of 1 to 3 millicuries per milliliter. The suspensions contained 200 T. U. of hyaluronidase and 0.01 ml. of 1–1000 epinephrine per milliliter. The doses ranged from 2 to 4 milliters containing 3 to 9 mc.

Mongrel dogs varying in weight from 9 to 20 kilos were used. Attempts were made to select old animals in order to obtain large prostate glands. Under pentobarbital anesthesia, the prostate glands were exposed through a midline suprapubic incision. The suspension of radioactive colloid was injected using a lead shielded syringe[1] similar to that described by Flocks' group[1] and a 2 inch 21 gauge hypodermic needle. One half of the total dose to be administered was infiltrated into each of the two halves of the gland. By moving the needle in and out of different areas while injecting an attempt was made to distribute the material as uniformly as possible through the prostatic parenchyma. Five to 10 minutes were required for the injection of each gland. After completion of the injection, the incision was closed in layers using cotton sutures and the animals

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Made possible by the Urological Research Fund and aided by funds obtained on contract AT(11-1)94 between Northwestern University and the U. S. Atomic Energy Commission.

* Markle Scholar in Medical Science.

† Flocks, R. H., Kerr, H. D., Elkins, H. B. and Culp, D.: Treatment of carcinoma of the prostate by interstitial radiation with radioactive gold (Au 198): A preliminary report. J. Urol., **68:** 510, 1952.

[1] Purchased from American Cystoscope Makers, Inc., New York, N. Y.

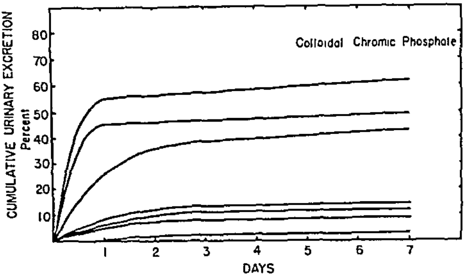

FIG. 1. *Cumulative urinary excretion of radioactive colloidal chromic phosphate following intraprostatic injection in dog.*

were placed in metabolic cages for collection of urine for radioactive assay. Blood samples were obtained at intervals for estimating the amount of radioactive colloid present in the circulation. Two weeks later in the case of chromic phosphate injection and one week later in the case of radiogold injection, dogs were sacrificed and samples of tissue obtained for studies on the distribution of the colloid in the body.

The amount of colloid in various tissues was estimated by homogenizing a weighed sample in 5 ml. of water in a glass homogenizer. In the case of the prostate gland, the entire organ was homogenized to avoid errors that might arise from unequal distribution. A suitable aliquot of the homogenate was pipetted into a cupped planchet and dried slowly under an infra red lamp. Plasma samples and diluted urine samples were pipetted directly into planchets and dried. The radioactivity was estimated by counting with an end window Geiger Meuller tube for a period sufficiently long to reduce the statistical error of counting to 2 per cent or less. All results were corrected for self absorption and decay. Previous studies on rat tissues have shown that these methods give recoveries of 90 to 105 per cent of the colloids added to homogenates of tissue.[2] Histologic studies on tissues removed from animals sacrificed at various time intervals following injection will be presented elsewhere.[3]

RESULTS

The data obtained on the urinary excretion of the radioactive colloids following intraprostatic injection are given in figures 1 and 2. Each curve represents an individual animal. The results for chromic phosphate show wide variation. Three animals which were injected with the same preparation of colloid on the same day excreted from 44 to 63 per cent of the administered dose in the first week. The other animals which were injected in groups of two with different preparations gave much lower excretions. These results may be due to a difference in particle size of one preparation or to a difference in injection technique not apparent at the time of injection.

Plasma concentration of the colloids was fairly constant over the 7 day period. The range of levels for animals receiving chromic phosphate (1.8 to 5.6×10^{-2}

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[2] Cooper, J. A. D. Unpublished data.

[3] Bulkley, G. J., Cooper, J. A. D. and O'Conor, V. J.: To be published.

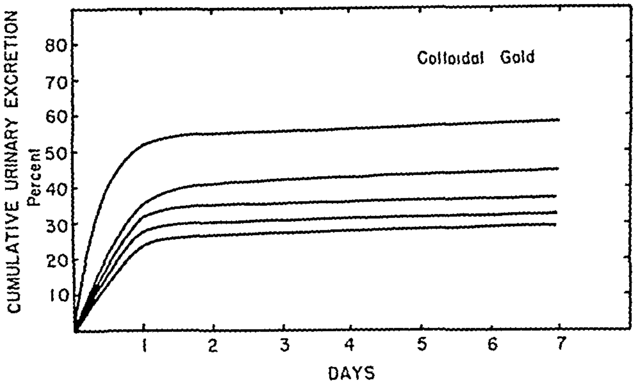

FIG. 2. Cumulative urinary excretion of radioactive colloidal gold following intraprostatic injection in dog.

TABLE 1. *Distribution of radioactive chromic phosphate and colloidal gold following intraprostatic injection in the dog*

ORGAN	CHROMIC PHOSPHATE		COLLOIDAL GOLD	
	%* per gram	% in total organ	% per gram	% in total organ
Prostate	.767	9.9	1.154	10.5
Liver	.023	10.6	.035	14.2
Spleen	.019	1.1	.005	0.2
Lung	.001	0.2	.002	0.2
Kidney	.001	0.1	.003	0.2
Bladder	.003	0.1	.001	0.02
Marrow	.018			
Lymph nodes	002		3.60	

* Per cent of the dose remaining in the body.

per cent of the dose administered per liter of plasma) was somewhat lower than that following gold (1.1 to 10.0 × 10^{-2} per cent per liter).

Data on the distribution of the colloids within the animal are presented in table 1 as per cent of the dose injected remaining in the body; the amount excreted in the urine has been subtracted from the dose administered. Average values for the content per gram of tissue and for the total organ obtained in six animals injected with chromic phosphate and 3 animals injected with gold are given.

DISCUSSION

The large urinary excretion during the first 24 hours probably results from the direct entrance of the colloid into the urethra and bladder from the prostate at the time of injection or shortly thereafter. In some of the animals a considerable amount of radioactivity was found in fluid stripped from the urethra immediately after completion of the injection. The small additional amount of activity which appears in the urine during the succeeding 24 hour periods may arise from excretion of the colloid present in the plasma by the kidney or by continued seepage into the urethra from the prostate. With the exception of the three animals aforementioned, a smaller excretion of chromic phosphate than gold occurred in the urine during the first week. This may be due to the larger particle size of chromic phosphate and its tendency to clump and form larger aggregates. No relation could be established between the size of the prostate gland or the amount of solution injected per gram of tissue and the total urinary excretion

The data obtained for urinary excretion in the dog cannot be used to predict excretion in patients receiving injections of the colloid for carcinoma of the prostate The difference in size, consistency and structure of the neoplastic human gland could result in entirely different excretion patterns Preliminary data on urinary excretion of patients who have received intraprostatic injections of radiogold indicate that much smaller amounts appear in the urine than are found for the dog

Since intravenously injected gold or chromic phosphate is rapidly removed from the circulation, the uniform plasma levels over a period of 7 days indicates a continual entrance of the colloids into the circulation from the prostate

The failure of the colloids to remain at the site of injection may be due to diffusion along the fascial planes of the pelvis In most cases less than half of the radioactivity can be accounted for in urinary excretion and the amount present in the organs and tissues studied Survey with a portable counter indicated that a large amount of radioactivity remained in the pelvis after removal of the prostate and urinary bladder It does not appear likely that all of the activity was present in the regional lymph nodes It should be pointed out that large amounts of hyaluronidase were used in the present experiments in an attempt to achieve uniform distribution in the gland Unlike the effects obtained in mammary carcinoma by Flocks and his coworkers,[1] we were unable to obtain satisfactory spreading in the prostate with hyaluronidase This is in agreement with Flocks' observations[4] that only about half of the biopsy specimens taken from patients previously injected with radiogold showed evidence of radiation reaction

The much greater concentration of radioactivity in the regional lymph nodes after the injection of gold as compared to chromic phosphate is noteworthy On autopsy, the nodes in the animals receiving chromic phosphate appeared normal while those in animals receiving colloidal gold were enlarged and hemorrhagic This difference is of importance since it would be desirable to obtain tumoricidal doses of radiation in the lymph nodes draining the prostatic area

The distribution of chromic phosphate and gold in various organs agrees with that reported for similar size particles administered intravenously[5, 6] The amount present in the liver was slightly higher in animals receiving radiogold, while the spleen contained more activity following injection of colloidal chromic phosphate A negligible amount was found in the lung, kidney and bladder

SUMMARY

Preliminary data on the excretion and distribution of radioactive colloidal chromic phosphate and colloidal radiogold after intraprostatic injection in dogs have been reported

720 N Michigan Ave , Chicago 11, Ill (V J O'C)

[4] Flocks, R H Personal communication

[5] Zilversmit, D B , Boyd, G A and Brucer M The effect of particle size on blood clearance and tissue distribution of radioactive gold colloids J Lab & Clin Med 40 255 19

[6] Jones, H B Wrobel C J and Lyons W R A method of distributing beta radiati to the reticulo endothelial system and adjacent tissues J Clin Invest , 23 783 1944

The method of injection and the preparation of the fluid to be injected are of importance in the attaining of adequate distribution.

It has been found that the transurethral route for injection was unsatisfactory for two reasons: 1) adequate placement in many suitable and necessary areas was impossible, and 2) contamination of the irrigating fluid was almost inevitable, with consequent danger of contamination of the operating surgeon and materials in the operating room.

The perineal route was only partially satisfactory. For the primary injection of small nodules, or for the secondary injection of small nodules which had escaped complete destruction following a primary treatment, this route was eminently satisfactory (figs. 1–3). However, it was not satisfactory in cases with rather large tumors because of inadequate exposure of the anterolateral areas about the prostate and the lack of exposure of the regional lymphatics.

For anatomicopathologic reasons, it was felt and demonstrated by India ink

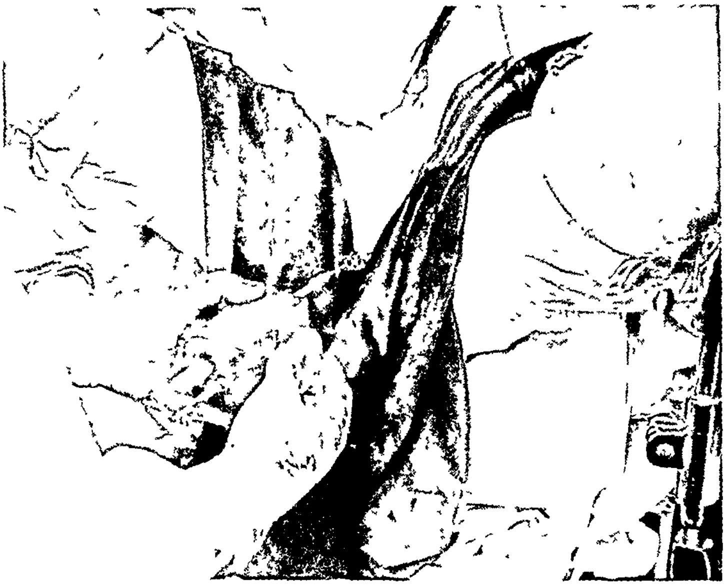

FIG. 3. Injection perineally using pressure syringe. Ordinarily about 4 or 5 cc are injected into each needle that has been placed perineally and total number of mc. is estimated upon mass of tissue involved. Usually not moie than 30 mc. are injected perineally at one sitting

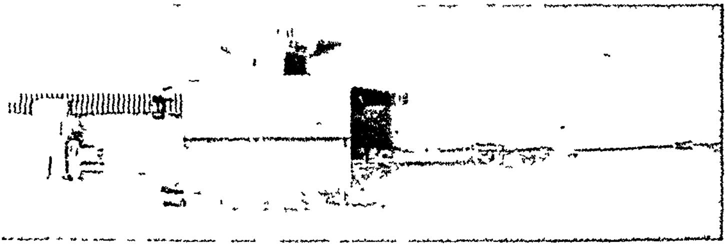

FIG. 4. Pressure syringe. Note lead protection. Note guard at end of needle which makes it impossible to push needle deeply into tissue. One depends upon dissemination of material through septa when it is injected under pressure. Not more than 1 cc is injected in each position so that all different fascial compartments may be covered. Most of features of this syringe are work of Dr. Elkins.

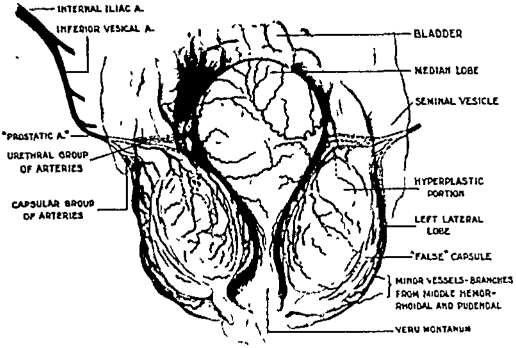

FIG. 5. Distribution of arteries within prostate. These simultaneously illustrate septal compartments in prostate and illustrate how, by several point injections at the vesical neck pointing needle distally, several septa and therefore several compartments can be covered. Since there is separate distribution to outer portion of gland, several injections should be made in outer portion, also pointing distally. Also, since as illustrated on sagittal section in figures 1 and 6, seminal vesicles and portion of prostate distal to verumontanum are in separate compartments, separate needle punctures must be made into these areas to obtain satisfactory injection.

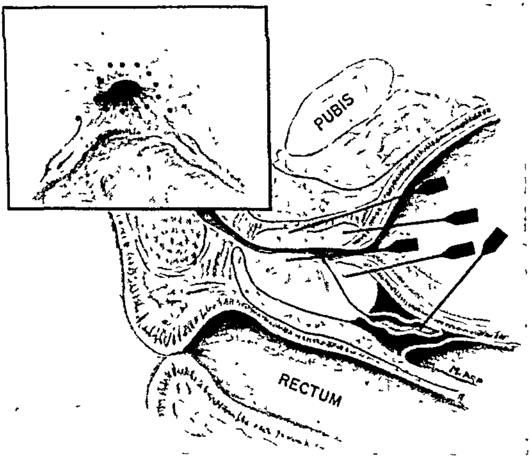

FIG. 6. Position of needles for injection transvesically. Note that each compartment is entered and 1 cc or more of material injected into it Similar injection is then made on outer side so that capsular areas are also infiltrated. This is done from vesical neck downward and distally on each side. Floor of prostatic urethra is injected by inserting needle into lumen of urethra and then pushing it into tissue, as illustrated. If one knows that most of carcinoma is in one area, several punctures are made in that area and several centimeters of material injected in that area so that area with most of tumor is well covered.

injections in cadavers, that the transvesical and retropubic routes of approach gave access to all the necessary fascial compartments, and when these are infiltrated under pressure with small volumes of solution satisfactory distribution of the material is possible (figs. 4–6).

The technique in the operation room is, therefore, as follows: The area is exposed suprapubically in the usual manner and all bleeding points controlled and the stab wound cystostomy performed. An estimate is made of the size of the gland with its tumor. The regional nodes are examined for metastases. This gives the dose in mcs. as described above. The number of injections and the total volume of solution to be used is then decided upon by the urologist in consultation with the radiologist. The following has been found to be most satisfactory: in glands 30–50 gm., 15–20 cc; in glands 50 or more gm. in weight, 20–30 cc are used. No more than 30 cc should be used. In the earlier cases, larger volumes were used with spread of the material away from the local area into fascial planes about the rectum, producing rectal damage and less radiation in the area of tumor. This material is deposited in each fascial compartment by separate injections as illustrated. Experience in the location and filling of these fascial compartments and in the installation of the material into dense nodular areas of carcinoma is necessary in order to obtain adequate distribution.

TABLE 1 *Summary First 100 cases of carcinoma of the prostate treated with Au*^{198}

	CASES 1–50 3–23–51 TO *1–18–52*	CASES 51–100 1–18–52 TO *7–3–52*	TOTAL OF 1ST 100 CASES
Age			
Average age	68.9	67.6	68.2
Median age	69.2	69.0	69.1
Previous treatment			
Transurethral resection	5	1	6
Stilbesterol	24	15	39
Orchiectomy	1	1	2
Premarin	0	1	1
Tase	0	2	2
Complications			
Total patients involved	15	3	18
Rectal irritation	13	1	14
Rectal bleeding	4	0	4
Rectal stricture	3	0	3
Rectal ulcer	4	0	4
Delayed wound healing	0	2	2
Urticarial hemorrhagic rash	0	1	1
Biopsy after gold			
Total patients biopsied	37	17	54
Negative biopsies	10	1	11
Results			
Alive without clinical disease	27	21	48
with clinical disease	8	24	32
Dead without clinical disease	7	1	8
with clinical disease	8	4	12

The radiologist is in the operating room and, as indicated above, consults with the surgeon with regard to dosage His prime duty is to prepare the colloidal Au^{198} from the stock solution by using the following diluents 100 units (1 cc) of hyaluronidase for each case, and a saline solution containing 1/100000 epinephrine He fills the pressure syringe and hands it to the surgeon who performs the actual injecting The radiologist also monitors all activities in the operating room relative to exposure of operating room personnel and disposal of contaminated drapes, sponges, etc , after each operative procedure

RESULTS

The results of this therapy in the first 100 cases are illustrated in table 1

SUMMARY AND COMMENT

Follow-up studies on the treatment of carcinoma of the prostate with interstitial radiation with radioactive gold in 100 cases, followed from 3 to 18 months, show the following points of interest 1) Negative biopsies have been obtained in a significant number of patients Clinical arrest has been obtained in 48 cases 2) With improvement in technique, particularly the use of the pressure syringe, the utilization of natural septa and fascial compartments to aid in the distribution of the material, the avoidance of long needle injections, and the diminution of the volume of material used (not the dosage)—the incidence of the complications, particularly the rectal difficulties, have been tremendously decreased In the first 50 cases 24 complications occurred This is to be compared with an incidence of 4 (all of a minor nature) complications in the second 50 cases 3) Secondary injections through a perineally placed needle are of value for the destruction of nodules which were not completely destroyed at the first sitting Such secondary injections, and even tertiary injections, keep the patient in the hospital for only a few days They should not be done earlier than three months after the preliminary injection, except in unusual circumstances where the surgeon has felt definitely that the preliminary injection did not produce adequate distribution They have proved of great value in many cases

As indicated in the preliminary report, further studies are being carried out along the lines of the utilization of beta radiation for the destruction of carcinoma of the prostate alone, and in combination with other types of therapy Our further experiences, which now include 1½ years of observation and 130 patients, have served to emphasize what was stated a year ago in the preliminary report "There is no question that even by the method used now tremendous destruction of the tumor, and in some cases apparently its complete eradication, has occurred, and secondly it is possible to give intensive radiation to carcinoma of the prostate by the techniques described without producing quantitatively the complications which have occurred in the past " It is also to be emphasized that only 1½ years have passed since we began our study, and it will take time to know the complete effects of this type of therapy in these cases

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BILATERAL CARCINOMA OF THE TESTIS: A REPORT OF THREE CASES

JAMES G. M. HARPER, STEPHEN B. DEWING AND GEORGE NAGAMATSU

From the Departments of Urology and Radiology, Veterans Administration Hospital, Bronx, New York, and the Department of Urology, Flower Fifth Avenue Hospital, New York, N. Y.

The incidence of testis cancer has been thoroughly investigated and discussed by Hamilton and Gilbert[1] and by Hotchkiss and Laury.[2]

The former reporters[1, 3] emphasized that when one testicle undergoes malignant change there is a significantly greater hazard of a tumor developing in its mate. This danger is so great that any patient who has had a testicular cancer requires close and indefinitely continued observation of his remaining gonad. There is general agreement that following treatment of a testis tumor the patient must be examined at short intervals for local recurrence and metastases but as yet there is no common recognition of the importance of continuing close observations long after the likelihood of recurrent disease is past. However, on the evidence of these workers, men who have had a testis tumor should be examined periodically as long as they live, not because of the danger of a tumor recurring after 5 or more years but because the remaining testis is an unusually great cancer risk.

The degree of this danger must be analyzed separately for patients with a) two scrotal testes, b) one ectopic testis, and c) two ectopic testes. Ectopy must be further subdivided into inguinal and abdominal cryptorchism. Since late correction has demonstrated no prophylactic value, a testicle which after puberty has been moved surgically from an ectopic to a scrotal position must be regarded as presenting the same hazard as one remaining undescended. The likelihood of a second testis tumor developing ranges from 0.7 per cent when both testes are scrotal, to 30 per cent when both are situated in the abdomen. The overall incidence of testicular cancer among men generally is only 0.0013 per cent.[1] It thus appears that the occurrence of a second neoplasm, even in men with two scrotal testes, is over 500 times as great as the incidence of a single tumor in men generally. When both testes are abdominal cryptorchids, the probability rises to 23000 times. It is evident that both glands then have little resistance to whatever the carcinogenic agent may be.

The growing literature of observed cases of bilateral testicular cancer should lead to a better understanding of the incidence of bilateral tumors, and possibly of the causative factors influencing their development.

There are now in the literature descriptions of 151 cases of bilateral testes tumors.[3, 4, 5, 6, 7, 8, 9] Because these records extend back as far as 1805 the ac-

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Accepted for publication April 24, 1953.

[1] Hamilton, J. B. and Gilbert, J. B.: Surg., Gynec. & Obst., 71: 731, 1940.

[2] Hotchkiss, R. S. and Laury, R. B., J. Urol., 63: 1086, 1950.

[3] Hamilton, J. B. and Gilbert, J. B.: Cancer Research, 21: 125, 1942.

[4] Graves, R. C. and Lawrence, K. B.: J. Urol., 37: 482, 1942.

[5] Smith, G. G.: J. Urol., 50: 585, 1943.

[6] Turkel, E. F. and Migliaccio, A. V.: Urol. & Cutan. Rev., 51: 42, 1947.

[7] Gill, R. and Howell, R. B.: J. Urol., 59: 940, 1948.

[8] Kaplan, G. and Roswit, B.: J.A.M.A., 144: 1557, 1950.

[9] Flynn, P. T. and Severance, A. O.: Cancer, 4: 817, 1951.

curate histological description of many is lacking. To these are now added three previously unreported cases from our records.

CASE REPORTS

Case 1. (Bronx VA Hospital No. 69343). In April 1943, while in the Army, a 26 year old white man first noted painless swelling of both testes. Both were removed 2 months later, in June 1943, in an army hospital and x-ray therapy was given to the abdomen during the succeeding month. Pathologic study revealed seminoma in both testes. He remained well, but a small left supraclavicular mass appeared 6 months later in December 1943, and metastases to the mediastinum and lungs were found in January 1944. Radiotherapy to the mediastinum and left supraclavicular region in the following two months caused regression of the masses and the patient was discharged in fair general condition. He returned to the hospital in November 1944, 17 months after orchiectomy because of recurrence of the left supraclavicular mass. He was also suffering from weakness, weight loss, and general malaise. Examination revealed new pulmonary foci of disease. Radiotherapy was again given (to the chest and left supraclavicular region) and moderate palliation of symptoms followed. His general condition progressively deteriorated however, and he died early in January 1945, 21 months after the tumors were first observed and 19 months after the tumors were removed.

Case 2. (Bronx VA Hospital No. 141187). A 25-year old white Norwegian seaman had a left orchiectomy in a Norwegian hospital in September 1946 for an "orange-sized" painless swelling of the testicle. Histological diagnosis was seminoma (fig. 1, *A*). A tumor dose of 2500 r was given to the left abdominal nodes and 1920 r to the left iliac nodes in four weeks, with a 1500 Kv unit. He remained well and at work until July 1951, when a painful swelling developed in the remaining right testicle. He was treated for orchitis until his admission to the Bronx VA Hospital, where on September 9, 1951, 2 months later, a right

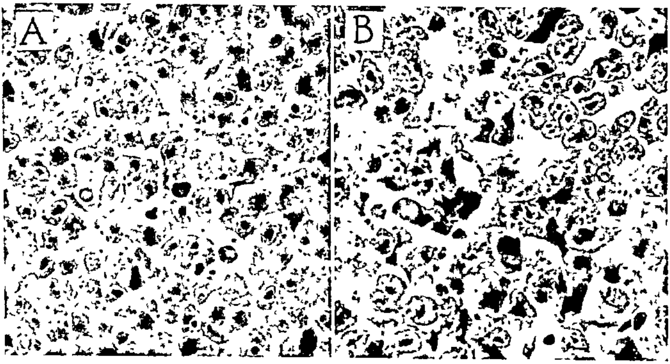

FIG. 1. Case 2. *A*, seminoma in left testis (× 475). *B*, embryonal carcinoma in right testis. (× 475)

orchiectomy was performed. The tumor was 5 cm. in diameter, and on histological examination proved to be an embryonal carcinoma (fig. 1, *B*).

At the time of the right orchiectomy solid "lucite" prostheses were placed in both scrotal cavities. Ten days following orchiectomy a right retroperitoneal node dissection was performed. Adequate exposure from the diaphragm to the femoral canal was gained by an incision from the tenth costovertebral angle to the groin with removal of one inch segments of the eleventh and twelfth ribs at their angles. The patient's trunk was rotated approximately 30 degrees during the operation to open the wound (fig. 2). Many small hard nodes were found densely adherent to the right common iliac vessels and aorta. On histological examination these proved to be metastatic embryonal carcinoma (fig. 3). As

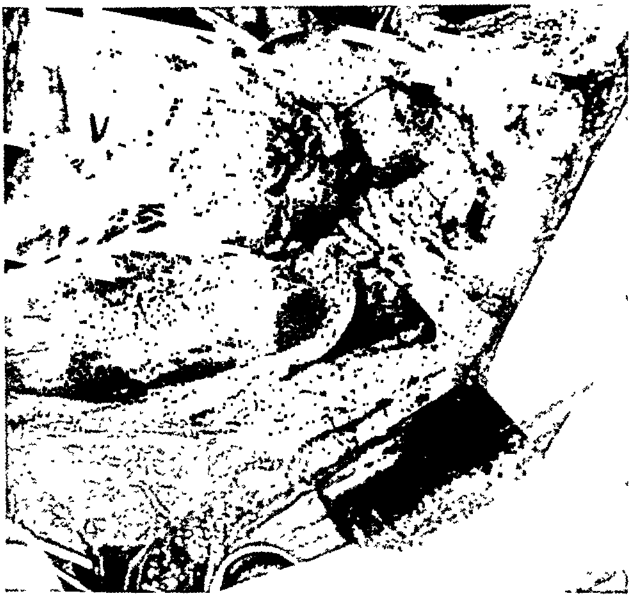

FIG. 2. Case 2. Operative wound showing exposure gained during right retroperitoneal node dissection.

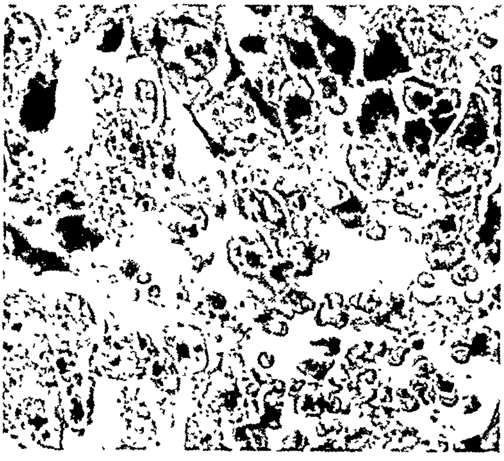

FIG. 3. Case 2. Metastasis in retroperitoneal node from right testis tumor. (× 475)

soon as his wound had healed the patient received a tumor dose of 2500 r to the region of the involved nodes through anterior and posterior portals in the upper and lower abdomen. The same dose was given to the right iliac fossa through a single anterior portal. Radiation factors were: 400 Kv unit, 5 milliamperes current, Thoraeus filter, HVL 4.7 mm Cu. On December 12, 1951 a left retroperitoneal exploration was performed and no tumor bearing nodes were found. He was discharged in good health, but a roentgenogram of the chest in February 1952, 7 months after the first symptom and 5 months after orchiectomy, revealed a large mass in the right side of the mediastinum.

Case 3. (Flower Fifth Avenue Hospital No 39-6504) A 32 year old white man entered Flower Fifth Avenue Hospital (New York City) in September 1939 because of a painless mass in the right testis noticed accidentally 2 weeks previously After 1 week's observation a right orchiectomy was done This testis

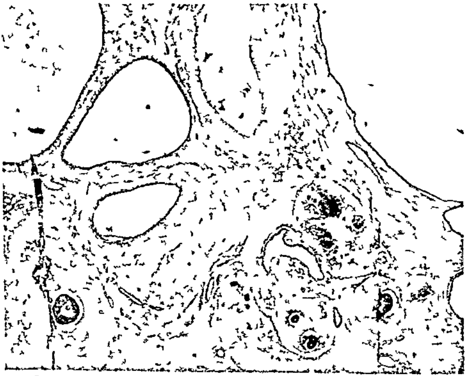

FIG 4 Case 3 Photomicrograph of teratoma in right testis (× 10)

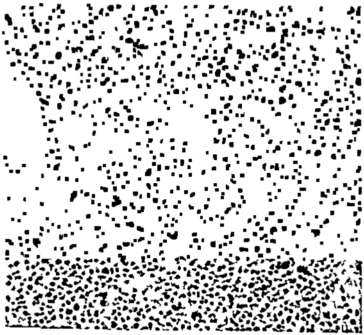

FIG 5 Case 3 Photomicrograph of embryonal carcinoma in left testis (× 100)

was found to be completely distorted by a tumor, measuring 9 by 6 by 5 cm. Gross section showed alternating areas of fleshy tumor, cysts, and hemorrhage. Microscopic study revealed a teratoma (fig. 4). For 12 years the patient remained well, but in April 1951 he re-appeared with a painless mass in the left testicle of 1 month's duration. Exploration revealed a tumor 7 by 5 by 5 cm. Orchiectomy was performed and the pathologic examination showed embryonal carcinoma (fig. 5). Postoperative radiation therapy was given the lymphatic drainage routes. In September 1951, 5 months later, persistent low back pain developed with anemia, anorexia, and general malaise. In November a large tender swelling appeared over the thyroid gland. In December enlarged supraclavicular nodes were noted on the left. His condition progressively deteriorated from September to December, when he died, 9 months after the tumor appeared and 8 months after it was removed.

DISCUSSION

Although simultaneous onset of bilateral testis tumors, as in case 1, may simplify diagnosis and lead to correct treatment, such an occurrence is by no means the rule. In most cases the tumors appear separately at intervals of a few months or several years. The intervening periods of 5 and 12 years respectively between the symptoms of the two tumors in cases 2 and 3 emphasize the fact that the time of observation must be unlimited. The longer single tumors are kept under observation, the more accurate will be the recognized incidence of bilateral tumors. Present therapy produces many cures of unilateral cancers. As a result patients who formerly succumbed may have a second tumor. Early diagnosis at a time when orchiectomy and radiation can produce a cure is essential. In certain cases of tumor, in which the remaining testis is known to be sterile because of atrophy or cryptorchidism after puberty, and where paternity is therefore impossible, careful consideration should be given to the prophylactic removal of the useless testis because it is likely to undergo malignant degeneration.

SUMMARY

The hazard of a second testis tumor developing is presented and emphasized. One hundred fifty one cases of bilateral tumor are cited from the literature and three previously unreported cases are described. The treatment of these cases was a combination of surgical and radiotherapeutic techniques. Careful observation following treatment of all patients with unilateral testicular cancer is urged. This should be continued indefinitely. Prophylactic orchiectomy is suggested when the remaining testis is sterile and presents a cancer risk.

We wish to express our appreciation to Consultant Archie L. Dean for sponsoring this publication.

5062 55th Place, San Diego 15, Calif. (J.G.M.H.)

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UROLOGICAL SURGERY IN COMBAT

Lt Col KRYDER E Van BUSKIRK (MC) and Col JAMES C KIMBROUGH (MC)

From Urology Section, Walter Reed Army Hospital, Washington, D C

This paper is based on the treatment of casualties observed at the 8076th Mobile Army Surgical Hospital from July 1950 to July 1951 During this period the hospital moved 23 times and recorded over 26,000 admissions It operated in summer heat well over 100F and winter temperatures ranging to 20° below zero Its relative position ranged from 6 to 30 miles from the front

The hospital could be in operation within four hours after its arrival in an area and could be packed and on its way in an equal length of time It was equipped with sufficient transportation to carry its entire personnel and equipment For approximately half of this period, the hospital was established in existing buildings such as schools, mills, or factories, and for the remainder of the time it was under canvas

The remarkable record of the Army Medical Service in Korea today is the result of closely integrated team work of medical service personnel working at all echelons All casualties, regardless of type, were given immediate first aid treatment as soon as possible after physical mishap occurred, and were removed to the Battalion Aid Station, which, under normal conditions was located within a half mile of the front

Treatment at this level was directed primarily toward preparing the patient for transportation to the rear This was accomplished, when indicated, by the prompt arrest of hemorrhage, proper splinting, judicious use of narcotics, antibiotics, blood derivatives, and in some instances, whole blood

As soon as the casualty was transportable, decision was made as to the type of evacuation to be employed Casualties not requiring further treatment for several hours were evacuated by litterjeep, or ambulance to the Regimental Medical Company, located about 2 miles further to the rear, and then on to the Division Clearing Station, 6 to 15 miles from the front Treatment enroute consisted of a continuation of that initiated in the battalion area

At this point, the patient whose condition contra-indicated further movement to the rear, was transferred to the Mobile Army Surgical Hospital, located in the immediate vicinity of, or adjacent to, the clearing station

In the Korean conflict, the helicopter has been utilized to transport seriously wounded patients directly from the Battalion Aid Station to the Mobile Army Surgical Hospital In a matter of minutes, the patient could be flown from the Battalion Aid Station to the Mobile Army Surgical Hospital where definitive emergency care was initiated If the customary medical evacuation chain had been followed, several hours would have elapsed before this same care could have been administered This time lag was due to the terrain and poor road network which make it impossible for an ambulance loaded with casualties to average

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Reading at annual meeting, American Urologic Association, St Louis, Mo , May 12, 1954 more than six miles per hour. The helicopter, in addition, has brought to surgery a new type of patient, one who in many instances could not have survived the trip over the customary medical evacuation chain. The helicopters also carried blood forward on missions, and upon arrival at the forward station, the blood transfusion was started, the casualty placed in the helicopter, and the infusion continued while the casualty was enroute to the hospital.

Upon arrival at the Mobile Army Surgical Hospital, the casualty was immediately seen by a doctor and thoroughly examined. The admitting diagnosis was confirmed, expanded, or revised, laboratory and/or x-ray studies ordered, and immediate treatment prescribed. As soon as this was accomplished, the patient was in reality on the assembly line—being transported by litter to the preoperative and shock treatment ward, stopping enroute for x-rays or laboratory work.

Upon arrival in the preoperative and shock ward, the necessary diagnostic procedures and treatment were begun and the patient prepared for surgery. Patients were then placed in the respective preoperative sections—head, chest, abdominal, or orthopedic—and the treatment, as outlined by the admitting officer, initiated by nurses and corpsmen. The patient was next seen by a surgeon who carefully evaluated his condition. With the supplemental diagnostic aids, laboratory, and x-ray results, the diagnosis was confirmed and the priority and time for surgery determined. The need for continued resuscitative and supportive measures was also decided at this time.

Routine treatment for patients in shock consisted of the use of shock blocks to elevate the foot of the litter, oxygen administered by nasal catheter, intravenous fluids, and whole blood. In general, if a patient failed to respond to two units of whole blood intravenously, the transfusion was discontinued by this route and given intra-arterially,[1] usually by inserting a 16 gauge needle into the brachial artery. The efficacy of this route, especially in patients with active internal hemorrhage or in profound shock, cannot be too highly recommended. A patient was considered ready for surgery when he had a systolic blood pressure of 110 or over and a pulse rate of less than 100.

Routine preoperative preparation in abdominal and chest cases—after the patient had reacted from shock—consisted of passing a Levine tube and the administration of intravenous preoperative medication. The anesthesia was given routinely by the endotracheal route to minimize inadvertent aspiration of stomach contents, since patients were seldom in a fasting state before the operation and coexistant thoraco abdominal wounds. If possible, a voided specimen of urine was obtained. If this was impossible, the patient was catheterized. If bloody urine was obtained, the catheter was left in place and serial collections of urine made to determine the increase or decrease in hemorrhage during the interval when the patient was being treated for shock.

As all previous observers have emphasized, and our observations were no exception, wounds which involved the genitourinary tract *per se*, were very uncommon[2] [3] Patients with wounds involving the kidney, ureter, and bladder were placed in the abdominal section Decision to operate was made almost entirely on such physical findings as rigidity, rebound tenderness, absence of peristalsis, and the manner in which the patient responded to shock treatment X-ray findings, such as obliteration of the psoas shadow, flexion of the spine, and a large soft tissue mass, or masses in either renal area, aided the surgeon in planning his operative procedure

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[1] Seeley, S. F.: Intra-arterial transfusion in shock. Current Res. Anesth., July–August, 1951, p. 195.

All operative procedures performed at this level were emergencies While definitive in the sense that they were life saving, they were not necessarily curative[4] Many of these patients required secondary procedures at a later date If the missile was easily accessible, it was removed No time was consumed trying to locate the foreign body, but the pathological change that it created was repaired Due to the shocked condition of the patient and the associated abdominal injuries excretory urography, as an aid to diagnosis, was not feasible As a result, other than observing the presence of hematuria, the exact diagnosis of upper tract change was usually made on the operating table

In nearly all cases, a bold, paramedian or rectus muscle splitting incision provided better exposure and was less time consuming than a transverse incision The abdomen, for general purposes, was divided into supracolic and infracolic regions The infracolic region was explored by inspecting the greater omentum and delivering it on a warm moist pack previously placed above the superior angle of the incision The small bowel was then explored, starting at the ileocecal junction with complete evisceration of the small bowel, until the ligament of Treitz was reached This maneuver afforded thorough inspection of the small bowel for possible perforations These were clamped with a Babcock clamp, thereby preventing further gross contamination and later serving as markers to enable the operator to decide on closure or resection It also afforded complete exposure of the leaves of the mesentery for perforation and bleeding vessels which, if present, were promptly secured By the foregoing procedure, the colic gutters were widely exposed and defects were easily visualized Visual inspection of the posterior abdominal wall and retroperitoneal structures were easily accomplished and the ureters exposed if changes were noted in the vicinity of their course The mobile portion of the sigmoid was inspected and the pelvic injuries evaluated

When the infracolic exploration was completed and the defects corrected, the contents were replaced and the supracolic organs explored, starting with the transverse colon, then the liver, gallbladder, stomach, and spleen If indicated, the lesser peritoneal sac was entered and explored While it is realized that evisceration is a shocking procedure, it is believed that this procedure is no more shocking then removing a few feet of bowel, replacing it, and then removing more. Furthermore, the operating time saved, and the more thorough visual exploration afforded, outweighs the disadvantages.

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[2] Young H H Wounds of the urogenital tract in modern warfare J Urol 47 59, 1942

[3] Kimbrough J C Urology in European theater of operations J Urol , 57 1105, 1947

[4] Management of Battle Casualties Dept of Army Technical Bulletin, p 147, June 22, 1951

In general, operative explorations in cases of gross hematuria were delayed until several serial urine specimens had been observed to determine the progression or regression of the hematuria. If the hematuria decreased and the patient required no further supportive therapy and it was certain the kidney was the only organ involved, the patient was treated expectantly. Unresponsive cases were explored, using a transperitoneal incision, since associated abdominal injuries were usually present. Routinely, the renal fossae were palpated to ascertain the presence and condition of both kidneys.

If on exploration of the abdomen for bowel trauma, after other abdominal changes had been corrected, a perirenal or retroperitoneal hematoma with no evidence of urinary extravasation associated with a decrease in hematuria was found, the perirenal space or retroperitoneal hematoma was not opened. If, however, hemorrhage was still active and, to prevent shock it was necessary to support the patient with blood, the involved area was always explored.

Nephrectomy was performed when the pedicle was shattered or the kidney was so severely damaged that repair was impractical.

When polar injuries were observed, segmental resection was performed. The superior or inferior poles were resected and a nephrostomy tube inserted. The viable surface was then closed with interrupted mattress sutures over fat pads, or with a running mattress suture, as described by Dees.[5]

Parenchymal repair was carried out in lacerations of the capsule, cortex, or pelvis. When indicated, a nephrostomy tube was always inserted to insure adequate drainage. All drains or tubes used were delivered to the exterior through a separate stab wound in the flank.

Ureteral injuries, partial or complete, were repaired over a splinting catheter. The splint extended from kidney to bladder with diversionary nephrostomy on the injured side.

Perforations of the lower third of the ureter were difficult to recognize, because of the almost universal presence of associated hematoma. If the perforation was suspected but not recognized, this area was drained retroperitoneally, using a Penrose drain through a separate stabwound.

When perforations of the bladder, extending intraperitoneally, were observed, the peritoneal laceration was enlarged and mobilized. The bladder defect or defects were closed extravesically, and the peritoneum closed in a separate layer over the defect. The abdominal procedure was then completed and the peritoneum closed. Following this the prevesical space was opened and a cystotomy performed. If necessary, further work was performed and the bladder closed about a cystotomy tube with a drain in the prevesicle space.

The management of vesical rectal wounds deserves special mention. In spite of antibiotics, the need for adequate drainage in vesicorectal wounds cannot be stressed too strongly Colostomy and suprapubic cystotomy with drainage of the prevesical space, alone, are not adequate It is also essential that these wounds be drained perineally with both ischiorectal fossae opened widely, and drains inserted to the site of the rectal perforation

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[5] Dees, J. E.: A set of needles for suturing the renal parenchyma. Surg., Gynec. & Obst., **78:** 409, 1944.

Extraperitoneal ruptures were usually associated with pelvic and perineal injuries, and while emergencies they were not in the acute emergency category as were the injuries previously described These were explored suprapubically Before entering the bladder, however, the peritoneum was opened and the lower abdomen explored The peritoneum was then closed and the bladder explored If feasible, the perforations were closed extravesically If too technically difficult to accomplish, they were closed intravesically In both methods, the bladder was closed over a cystotomy tube, and drains inserted in the prevesical space

In wounds of the scrotum, penis, and perineum, before débridement was attempted, an 18 or 20 Foley catheter was passed to the bladder and left indwelling This aided in recognizing partial defects which could easily be closed If, however, a catheter could not be passed, the defects were explored when débridement was carried out A sound or catheter was passed through the urethral meatus to aid in identifying the distal segment of the urethra This portion of the procedure usually offered no difficulty However, in injuries to the bulbous, membranous, and prostatic portions of the urethra, this was usually accomplished with some difficulty, due to lateral displacement in the bulbous urethra and upward displacement in the membranous or prostatic urethra Locating the proximal segment of the urethra can be greatly facilitated by sponging the area well and exerting suprapubic pressure, which results in a flow of urine from the severed proximal portion Almost invariably associated pelvic fractures would be found Anastomosis here was accomplished with mattress sutures brought out through the perineal muscles, as employed in radical perineal prostatectomy or anastomosing bladder neck to urethra In all cases of urethral anastomosis, temporary diversion of the urinary stream was accomplished If the transection of the urethra was distal to the bulb, a perineal urethrostomy was performed and the splinting catheter brought out through the same opening as the tube If proximal to the bulb, the urethral splint went from the urethral meatus to the bladder, and a suprapubic cystotomy was performed In all cases of suprapubic cystotomy, the prevesical space was drained

In one instance the penis was entirely denuded Debridement was carried out, the scrotum incised along the median raphe, and the flaps dissected free The penis was then buried in the scrotum Injuries of this type were usually associated with multiple wounds of the lower abdomen, perineum, and thighs, and caused by fragmentation missiles

Wounds of the scrotum were debrided and the skin edges approximated loosely over a rubber drain

In wounds of the testicle, with the blood supply intact, debridement and closure of the tunica albuginea were accomplished When one or both testicles were so damaged that repair was not practical, orchiectomy was performed. The scrotal sac was always drained.

CASE REPORTS

Case 1. A 24-year-old lieutenant was admitted with a through-and-through gunshot wound of the upper abdomen. The entrance was 5 cm. to the left of the midline, midway between the umbilicus and the xiphoid. The exit wound was in the eleventh interspace, 6 cm. to the left of the spinous processes. On exploration, the patient was found to have a through-and-through perforation of the stomach, fractured spleen, four perforations of the splenic flexure of the colon, perforation of the diaphragm, and a shattered superior pole of the left kidney. The remaining portion of the kidney was pale, contracted, and very avascular. A splenectomy, left nephrectomy, closure of the perforations of the stomach and diaphragm, and exteriorization of the splenic flexure of the colon were done.

Case 2. A 23-year-old soldier was admitted in profound shock with a gunshot wound. The bullet had entered the right midaxillary line 2 cm. inferior to the tip of the twelfth rib and made its exit in the left posterior axillary line at the level of the eleventh rib. A moderate amount of blood was emerging from the exit wound. A catheterized specimen contained markedly bloody urine which clotted in the container. The patient failed to respond to intravenous transfusions, but responded to intra-arterial transfusion. Exploration revealed an extensive left perirenal hematoma. Fluid was observed in the area of the right renal pedicle but no hemorrhage was noted. A defect in the body of the second lumbar vertebra was also found. The upper third of the left kidney was completely severed. A nephrostomy, with splinting catheter down the ureter, was accomplished and the repair was completed with a continuous mattress suture over fat pads. The right renal pelvis was completely severed from the right kidney. A nephrostomy was performed and the pelvis re-anastomosed.

Case 3. A 26-year-old soldier was admitted with a gunshot wound which had entered the left lower abdomen midway between the left anterior superior iliac spine and the umbilicus, and exited posteriorly 4 cm. to the left of the midline at the level of the fourth lumbar vertebra. On exploration three small bowel perforations and a completely severed left ureter were found. The perforations were repaired and the abdomen closed. The patient was then placed in the left kidney position and through a left flank incision, a splinting ureteral catheter was passed from the renal pelvis through the free end of the ureter into the bladder, and primary anastomosis of the ureter accomplished. A left nephrostomy completed the procedure.

Case 4. A 36-year-old soldier was admitted with multiple superficial appearing wounds of the lower abdomen and right thigh; symptoms of bowel trauma were present. X-ray revealed an irregularly shaped foreign body 1 by 2.5 cm. lying in the midline 3 cm. below the superior border of the sacrum. Abdominal exploration revealed a rent in the ileum with the foreign body in the lumen, and an intraperitoneal perforation of the bladder. The foreign body was removed and the bowel closed. The bladder defect was closed extravesically and peritonealized.

The peritoneum was closed and the prevesical space explored, revealing a perforation of the right anterolateral wall of the bladder which was closed extravesically A cystotomy was performed, but no further injury was revealed The cystotomy was closed around a large catheter The prevesical space was drained

Case 5 A 33 year old soldier arrived with multiple shell wounds of the buttock and posterior thigh Examination disclosed a defect in the left rectal wall above the internal sphincter Cystoscopy revealed a perforation in the trigone midway between both ureteral orifices, and a defect in the right lateral wall of the bladder The ischiorectal fossae were opened wide, drains inserted, and a transverse colostomy was performed The only positive finding at the time of exploration was a large hematoma underlying the pelvic peritoneum After the peritoneum was closed, the prevesical space was opened and a shell fragment was recovered from the right prevesical space A cystotomy was accomplished and the defect in the trigone closed intravesically The defect in the right lateral wall was closed extravesically The bladder was drained with a cystostomy tube, and the prevesical space with a Penrose drain

Case 6 A 22 year old soldier was admitted with a gunshot wound entering the left buttock and exiting in the right groin 2 cm below the medial third of the inguinal ligament The patient was unable to void and could not be catheterized An inverted U incision was made in the perineum, the apex of the incision being 2 cm anterior to the anal mucocutaneous junction The urethra was completely severed in its membranous portion, and there was laceration of the deep transverse perineal muscle Anastomosis of the torn ends of the urethra was accomplished over a splinting catheter Mattress sutures were tied over the perineal muscles A diversionary suprapubic cystotomy was performed

Case 7 A soldier was admitted to the hospital with multiple shell fragment wounds of the right thigh, scrotum, and perineum The right testicle was fractured and lying on the posterior scrotal surface There was a deep laceration of the ventral surface of the penis just distal to the penoscrotal junction The vascular supply to the right testicle appeared to be intact The herniated testicular tissue was excised and the tunica albuginea closed The scrotum was débrided and the testicle replaced A drain was then inserted and the scrotum closed The penile urethra was severed just distal to the penoscrotal junction This was anastomosed over a splinting catheter which was brought out through a perineal urethrostomy The urinary stream was diverted by catheter through the perineal urethrostomy

COMMENT

In forward areas, the early recognition and proper management of urological injuries will prevent many unnecessary complications and minimize difficult secondary procedures

It is essential that the surgeon assigned to Mobile Army Surgical Hospital units be well grounded not only in the principles of general surgery, but also in surgical subspecialties and should be capable of coping with any condition requiring surgery.

Traumatic injuries of the genito-urinary tract per se are so infrequent that the presence of a urologist to perform urological surgery alone is not justified.

It is essential that surgeons assigned to forward units be general surgeons in the broadest sense of the word.

SUMMARY

The manner in which injuries of the genito-urinary tract were treated in the 8076 Mobile Army Surgical Hospital has been outlined.

Illustrative cases are presented.

The helicopter has greatly reduced the time interval between physical mishap and surgical care, thereby bringing a new group of severely injured patients to surgery.

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RAPID IDENTIFICATION OF URINARY CALCULI THROUGH USE OF X-RAY ANALYSIS

W. J. SMOTHERS and L. H. SIEGEL

From Institute of Science and Technology, University of Arkansas, Fayetteville, Ark.

The identification of materials forming a urinary calculus is of value because, depending upon its composition, either certain dietary changes can be made, or medicinals prescribed which will reduce the probability of further calculus formation. Almost all calculi are crystalline and therefore possess definite physical properties.

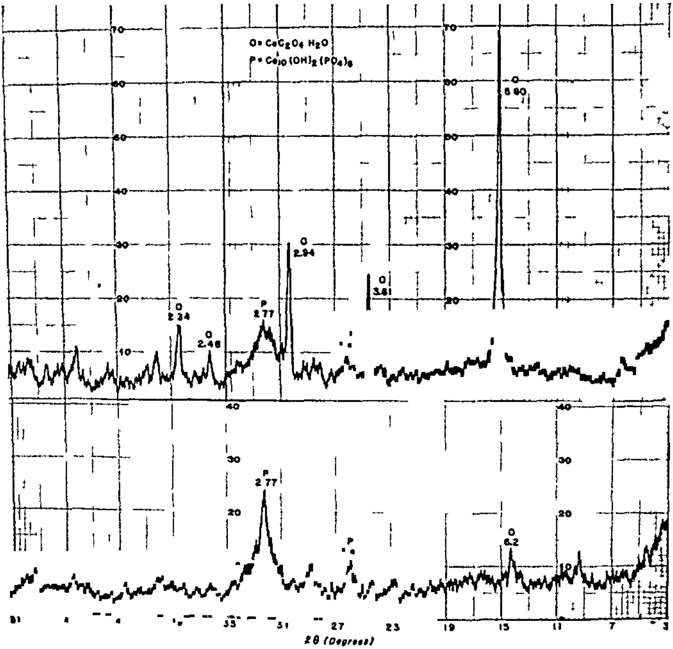

Fig. 1. X-ray powder patterns of urinary calculi. Upper diagram, calculus predominantly oxalate; lower diagram, calculus predominantly phosphate.

As recently as 1943, Higgins[1] called attention to the need for a simple, and yet accurate, method by which renal calculi may be qualitatively analyzed. Chemical analysis has been used for many years and a recent paper discussed

Accepted for publication May 1, 1953.

[1] Higgins, C. C.: Renal Lithiasis. Springfield: C. C Thomas, 1943, p. 53.

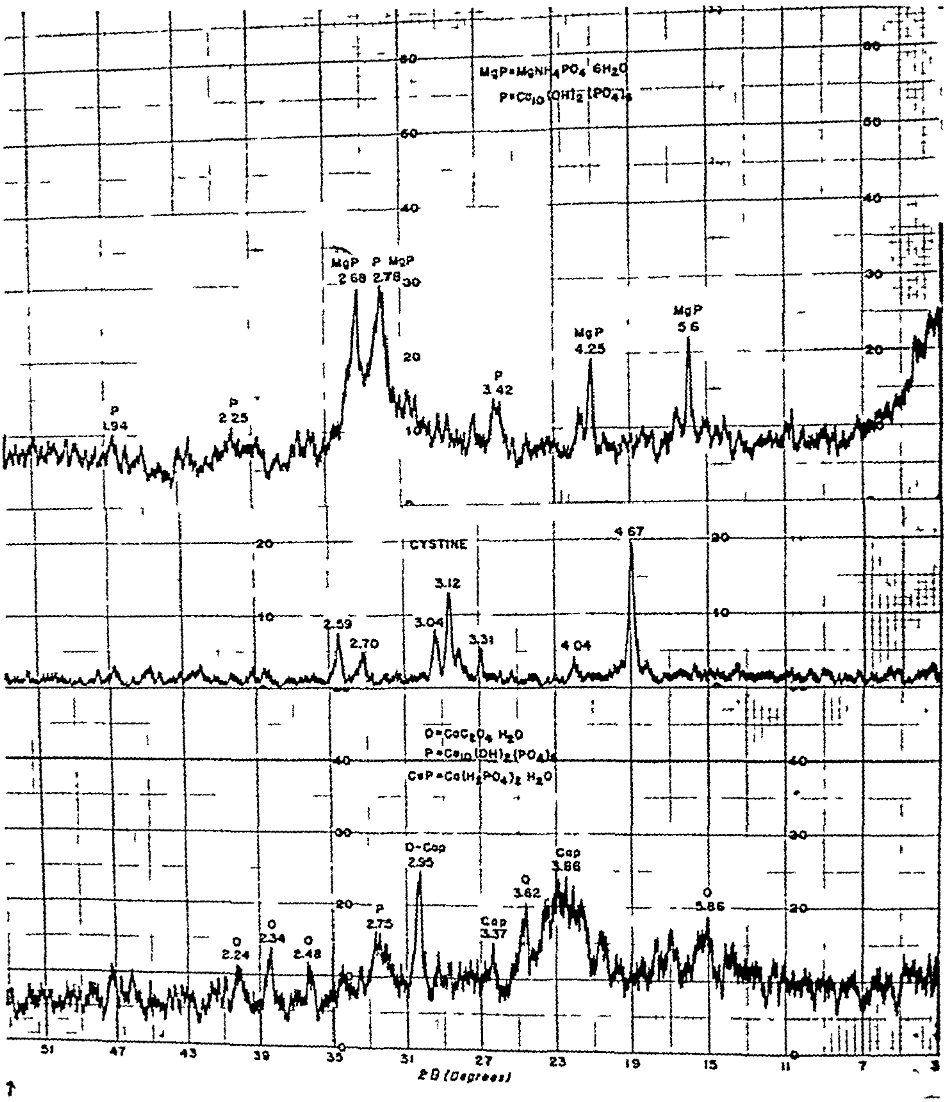

FIG 2 X-ray powder patterns of urinary calculi Upper diagram, calculus mixed phosphates Middle diagram, calculus cystine. Lower diagram, calculus phosphate and oxalate.

the use of microscopic methods which are ordinarily used to study minerals.[2] This same paper shows the use of the x-ray camera for identification of renal calculi.

Recent improvements in x-ray equipment have eliminated the need for film use in many cases. A Geiger tube which scans the diffraction arc is used to register the positions and intensities of the diffracted beams. The time required to analyze a calculi through use of x-ray film is approximately 2 to 3 hours while satisfactory results through use of the Geiger tube arrangement can be obtained in approximately 15 to 45 minutes. Identification of the components is possible through correlation of the x-ray pattern with those recorded in a file prepared by the American Society of Testing Materials.

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[2] Prien, E. L and Frondel, C.: Studies in urolithiasis. J. Urol., 57: 949–91, 1947.

The crystalline substances found to be present in urinary calculi by Prien and Frondel[2] were: oxalates, phosphates, uric acid, urates and cystine. From the literature, xanthine and indigo are also to be expected. Oxalate and oxalate-phosphate calculi are usually found in acid sterile urine while phosphate calculi are usually found in alkaline infected urine.

Several human urinary calculi were obtained and powdered in an agate mortar before placing in the sample holder for x-ray analysis. Powder patterns were obtained and analyzed (figs. 1 and 2). Results showed 2 calculi consisting of oxalate, 3 of mixed oxalate and phosphate, 1 of phosphate, and 1 of cystine. *Prien and Frondel*[2] *examined approximately 700 calculi and found 36 per cent* consisting of oxalate, 32 per cent of mixed oxalate and phosphate, 20 per cent of phosphate, and 12 per cent of uric acid or cystine. With the extremely small number of samples investigated in this study (seven), the comparison of these results with those of the more comprehensive study is striking.

To the authors' knowledge, the identification of $Ca(H_2PO_4)_2 \cdot 2H_2O$ (fig. 2) in urinary calculi has not been previously reported.

SUMMARY

Use of x-ray analysis, as aided by recently designed auxiliary equipment, has produced qualitative and semiquantitative data more quickly than other means commonly used for analyzing urinary calculi.

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FURADANTIN

GRAYSON CARROLL AND ROBERT V. BRENNAN
Department of Urology, St. Louis University, St. Louis, Mo.

Nitrofurantoin (Furadantin) is a new chemotherapeutic agent recently accepted by the Council on Pharmacy and Chemistry of the American Medical Association for acceptance. It was detailed to the urologists recently and is now available commercially.

This drug was preceded by Furacin, made popular during World War II, as a bactericidal agent used only for local application. Furadantin is designed for oral administration and is absorbed promptly by the intestine, appearing in the urine in one-half hour after ingestion. Forty-four per cent is recovered in the urine in eight hours, only 4 per cent being recovered in the feces. This suggests its peculiar adaptation for use in bacterial infections of the urinary tract.

We wish to make a preliminary report of our laboratory and clinical studies concerning the tolerance, toxicity and effectiveness of this new drug, Furadantin.

TOLERANCE

The only untoward symptoms noted in patients administered the drug were nausea, and to a lesser degree, vomiting. Dizziness, headache, diarrhea, itching, parasthesia, often seen as side reactions with other drugs, have not been observed in patients taking Furadantin.

A diffuse maculo papular eruption over the chest and arms appeared in one patient taking Furadantin. This was thought to be the result of the medication, inasmuch as it disappeared when the drug was withdrawn. This is the only instance in the 128 patients observed by us.

Nausea appeared in 33 per cent of the patients and vomiting in less than 1 per cent. These symptoms were promptly relieved when the drug was withdrawn and, in some instances, when the dosage was reduced. These symptoms were also avoided or lessened by the administration of the drug with food or after meals, and the giving of alkalis. Since some patients complained of nausea after only three doses of a 100 mg. tablet, it is felt that the reduction of the dose is not always the answer.

TOXICITY

No marked toxic effects have been noted. Two patients under our observation took the drug for 25 and 35 days respectively with no untoward effects. Careful examination of the blood, made before and after ingestion, has revealed no changes in the blood picture. Repeated urine analyses during the course of treatment failed to reveal any appearance of albumin or red blood cells. Nonprotein nitrogen determinations, made before and after treatment, showed no appreciable change.

This investigation was made possible by a grant from the Olin Foundation. The clinical and laboratory work performed at St. John's Hospital, The drug furnished by Eaton Laboratories, Inc.
Read at annual meeting, American Urological Association, St. Louis, Mo. May 12, 1953.

TABLE 1 *Furadantin liver studies*

	BEFORE			AFTER				
Patient	B S P % Retention	C C Flocc	Van d bgh mg % bilirubin	Dosage		B S P % Retention	C C Flocc	Van d bgh mg % bilirubin
1	40	Neg	6	600 mg for	8 days	24	Neg	6
2	0	Neg	2 5	500	5	0	Neg	45
3	1	2+	1 7	600	3	4	1+	1 2
4	0	Neg	75	600	11	3	Neg	75
5	16	Neg	1 2	600	3	9	Neg	1 2
6	3	1+	1 5	600	3	22	Neg	1 5
7	1	1+	75	600	9	3	Neg	75
8	48	Neg	1 2	600	9	15	Neg	3
9	0	1+	1 0	600	9	4	2+	50
10	12	Neg	6	500	9	12	Neg	75
11	5	3+	1 0	600	6	7	Neg	1 0
12	4	Neg	12	600	3	4	Neg	325
13	11	3+	5	500	11	3	1+	50
14	0	Neg	25	500	8	18	1+	75
15	10	Neg	2 0	500	10	2	1+	1 5

Fifteen patients were studied for possible liver damage (table 1) Liver function tests, consisting of the bromsulfalein, Van den Bergh, and cephalin flocculation tests, were made on each patient prior to the administration of the drug and at the conclusion of treatment, which averaged 7 days of 500 mg of Furadantin daily The tests show no appreciable change In the patient taking 600 mg daily for 35 days, the bromsulfalein test showed 12 per cent retention, which is a high normal

Since the drug has a nitro ring, particular attention was given to the possibility of testicular suppression The investigators at the Eaton Laboratories report that the seminiferous tubules in rats who had been given enormous doses of Furadantin, showed atrophy, but when the drug was withdrawn the normal tissue reappeared This was thought to be a metabolic arrest, rather than a toxic effect

We studied the testicles which had been removed from three patients who had been on normal doses of Furadantin (500 mg daily) for 9 days The testicle in one patient showed atrophy and the other two showed spermatogenesis All of these patients were elderly, having carcinoma of the prostate No studies of ejaculated seminal fluid before and after drug administration have been made

BLOOD LEVELS

Blood level determinations on patients taking Furadantin were determined by the method described by H Paul and F Popko * The principle of this test is that the drug is determined by measurement of its absorption in the ultraviolet spectrum after separation in 95 per cent alcohol solution from lyophilized blood

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* Reported at the 116th meeting of the American Chemical Society, Atlantic City, N J September, 1949

The average blood level was observed to be 2.23 mg. per liter in patients receiving the recommended dose of 5 to 7 mg. per kilogram weight or 500 to 600 mg. daily. The peak of the blood level was attained on an average of 2 hours after ingestion. The highest concentration observed was 5.64 mg. per liter 2 hours after the patient had received 600 mg. in one dose. This dose caused nausea and vomiting and is probably the maximum amount that can be administered.

Apparently there is no accumulation of the drug since 6 patients taking the average dose over a long period of time showed no increase in blood level. One patient taking the drug for forty consecutive days still had a level of 2.92 mg. per liter.

High blood levels were not observed in patients with impaired renal function, as exemplified by Mr. A. E., who maintained a nonprotein nitrogen of 54 and a phenolsulfonphthalein of 20 per cent. The blood level 2 hours after taking 400 mg. of Furadantin was 1.6 mg. per liter and was 2.72 mg. per liter in 4 hours. In 24 hours after the medication was administered, there was no evidence of the drug in the blood.

EFFECTIVENESS

Sensitivity tests. The sensitivity tests made by the tube dilution method on 170 strains isolated from current urinary infections, gave the results as recorded in tables 2 and 3.

Table 2 represents the results when an inhibition blood level of 7½ mg. is used, which would indicate that Escherichia coli, Escherichia intermediate and Streptococcus fecalis are inhibited and to a less degree, Aerobacter aerogenes and Proteus.

In table 3, the higher inhibitory blood level is taken of 15 mg. which would indicate that Escherichia coli, Escherichia intermediate, Aerobacter aerogenes, Paracolon coliforme, Proteus vulgaris, Alcaligenes fecalis, and Streptococcus fecalis are susceptible. Our clinical experience would indicate that the latter inhibitory blood level is reliable.

Clinical study. The clinical study is recorded in table 4. A rather rigid criterion

TABLE 2. *Furadantin sensitivities*

ORGANISM	INHIBITED*	NOT INHIBITED
Escherichia coli	39	0
Escherichia intermediate	7	4
Aerobacter aerogenes	4	8
Paracolon coliform	1	3
Pseudomonas aeruginosa	0	40
Proteus vulgaris	10	18
Alcaligenes fecalis	2	4
Enterococcus (Streptococcus fecalis)	11	0
Staphylococcus	19	0
Total	93	77

* Minimal inhibition concentration less than 7.5 mg.%

TABLE 3. *Furadantin sensitivities*

ORGANISM	INHIBITED*	NOT INHIBITED
Escherichia coli	39	0
Escherichia intermediate	10	1
Aerobacter aerogenes	11	1
Paracolon coliforme	3	1
Pseudomonas aeruginosa	0	40
Proteus vulgaris	27	1
Alcaligenes fecalis	5	1
Enterococcus (Streptococcus fecalis)	11	0
Staphylococcus	19	0
Total	125	45

* Minimal inhibition concentration less than 15 mg.%

TABLE 4. *Furadantin, clinical*

ORGANISM	CONTROLLED	NOT CONTROLLED
Escherichia coli	32	1
Escherichia intermediate	0	0
Aerobacter aerogenes	6	2
Paracolon coliform	0	0
Pseudomonas aeruginosa	1	21
Proteus vulgaris	9	1
Alcaligenes fecalis	2	1
Enterococcus (Streptococcus fecalis)	1	0
Staphylococcus	1	0
Fungus	1	0
Total	53	26

was set up in this group; namely, only two results recorded: "controlled" and "not controlled" An infection was considered controlled only when one or more *cultures of the urine were negative. Symptomatic improvement or lessened* degree of pus or bacteria in the urine was not considered controlled. The majority of these patients were in the hospital and included a large variety of infections, chronic in nature.

It would appear from this study that the drug is useful in infections caused by the Escherichia coli, Aerobacter aerogenes, Proteus, Alcaligenes, Streptococcus fecalis and staphylococcus.

Its effectiveness in Proteus infections has been most encouraging and valuable since the Proteus causes *recurrent stone formation and encrustations. Any* persistent alkaline urine is usually Proteus or staphylococcus.

The effect on Pseudomonas infections, both in our laboratory and clinical findings, has been disappointing. Some of the patients having Pseudomonas infection have been given the drug for 25 to 35 days with doses as high as 600 to 800 mg. daily, and yet the cultures have remained positive.

CONCLUSIONS

This preliminary study would indicate that Furadantin is a useful chemotherapeutic agent in the treatment of urinary infections and will be a valuable addition to our therapeutic agents, particularly useful in the stubborn Proteus infections.

No toxic effects were found in 128 patients observed. Urine analyses, nonprotein nitrogen determinations, liver function tests, testicular biopsies, blood studies, failed to reveal any serious alteration of liver, kidneys, hematapoetic system and testicular tissue. Nausea was observed in one-third of the patients; vomiting in 1 per cent; diarrhea, itching, and allergic reactions were not observed; skin eruption noted in 1 patient.

Furadantin was found to be effective in the majority of strains of Escherichia coli, bacillus proteus, Aerobacter aerogenes, Streptococcus fecalis and Alcaligenes. It was observed to be ineffective against the Pseudomonas aeruginosa.

The study of this drug indicates the fact which we have repeatedly emphasized; that is, the necessity of selecting the proper drug for the infecting organism, which must be identified and isolated in resistant infections. New drugs are necessary to combat the surviving strains from other medications, since these strains soon become the dominant infecting organism.

609 Humboldt Bldg., St. Louis 3, Mo.

The Journal of Urology
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THIOSULFIL FOR CHRONIC URINARY TRACT INFECTIONS

ROGER W. BARNES

From the Department of Surgery (Urology), School of Medicine, College of Medical Evangelists, Los Angeles, Calif.

Thiosulfil was used in 38 cases of chronic urinary tract infection in which adequate follow up data were obtained. Most of these patients had been under treatment for many months and had been given other anti infection medication with no benefit or only temporary clearing of the urine or relief of symptoms.

The cause of the infection in 25 cases was residual urine due to lower urinary tract disease, which for some reason could not be eliminated, such as prostatic carcinoma or hypertrophy (16 cases), vesical diverticulum or hypotonia (6 cases). Chronic upper urinary tract infection was present in 22 cases, some of which were secondary to the lower tract obstructive lesions.

The predominant organism was E. coli communior. Five other organisms were identified by culture.

The dose in most cases was 2 tablets (.5 gm.) q.i.d. for 5 days, then 1 tablet (.25 gm.) q.i.d. for the remainder of the time of medication, a few took one tablet (.25 gm.) b.i.d. The total amount taken was as follows: One case less than 100 tablets (25 gm.), 36 cases 100 to 500 tablets (25 to 125 gm.), one case more than 500 tablets (125 gm.). The length of time of medication was: 1 case less than 2 weeks, 24 cases, 2 to 6 weeks, 13 cases, more than 6 weeks.

The results of treatment were as follows: Good, 17 cases, urine became clear and symptoms subsided while under treatment; fair, 10 cases, infection reduced and symptoms became less or subsided; poor, 11 cases, no evident change in urine or symptoms. Results were not consistently poor with any one type of organism except that the only case of A. aerogenes was in this group. Six of this group of poor results had previous anti infection drugs without benefit.

Untoward reactions to Thiosulfil were few. One patient complained that her stomach and eyes burned and her head was thick so that medication was discontinued. One was somewhat dizzy and had slight itching, one had slight diarrhea. There were no other untoward reactions even though many patients previously had unfavorable reactions to other anti infection agents. Complete blood counts were done on 10 patients after they had been on Thiosulfil for from 2 to 6 weeks. There was no evidence that the drug made any change in the blood count.

SUMMARY AND CONCLUSIONS

Thiosulfil gave beneficial results in 75 per cent of 38 cases of chronic urinary tract infections, most of which had not responded, or had unfavorable reactions to other anti infection drugs. It is useful for palliation in chronic urinary tract infections that are due to pathological conditions which cannot be cured. The drug can be taken over a long period of time with practically no untoward side reactions.

1216 Wilshire Blvd., Los Angeles 17, Calif.

Accepted for publication April 10, 1953.

Thiosulfil (Ayerst McKenna & Harrison) is the sulfonamide, 2 sulphanilamide, 5 methyl, 1 3 4 thiodiazole.

and an actual resection of the clot using the direct vision Thompson resectoscope. In each case the clot was, as in the first patient, grayish white and firm, in consistency similar to the tissue of benign prostatic hypertrophy, and in each was about the size of a golf ball.

It occurred to us that perhaps irrigating with saline might be washing away the red blood cells but leaving fibrin to form a mass which could give subsequent difficulty. We have all had experience with the formation of a hard clot in the bladder following irrigation through a catheter postoperatively. Apparently the saline contributes to the firmness of the clot. The dark color is due to the hemoglobin. It was not until we observed these three patients cited, who had a grayish white fibrin clot of good size, that we became aware of its significance. We then realized that if, instead of using saline, we employed some other solution, one which would not so firmly precipitate the fibrin, we might avoid this difficulty.

Accordingly, Cytal solution was used to irrigate indwelling catheters postoperatively for transurethral resection of the prostate and of bladder tumors. It was found that whereas in using saline one was required to irrigate the catheter, for example every 15 minutes, using the diluted Cytal, one need irrigate the bladder only every hour to an hour and a half or even longer. It was found that with this solution the aspirated material returns a smoky red color rather than the usual red color as when saline is used. It is also free of any firm clots. Among patients who had postoperative bleeding after the catheter had been removed and had to be replaced, frequently clots were present in the bladder. A concentrated solution of Cytal softened these clots and made it possible to evacuate them completely; whereas, using saline, the clots would remain firm enough so that they would not come through a rubber catheter and would require an anesthetic and evacuation of the clots in the operating room. We consider this a distinct advantage from the standpoint of safety to the patient. We have, therefore, used this solution more or less routinely in the management of postoperative irrigation in the transurethral resection of the prostate and of transurethral resection for bladder tumors.

We have recently used Cytal in a series of 10 patients who had suprapubic prostatectomy and enucleation of the gland with a primary closure of the bladder. A polyethylene drain was left down to the closure of the bladder and brought out suprapubically, and a catheter was inserted from below and managed exactly as a transurethral resection.

In one of these patients subsequent postoperative hemorrhage developed, and it was necessary to return the patient to the operating room on his fourth day and fulgurate the arterial bleeder transurethrally exactly as in a transurethral resection. This was accomplished without difficulty, using the Cytal solution during the procedure as well as afterwards; and in these patients there was no suprapubic drainage of urine. The wound healed primarily; there was no evidence of irritation, and no apparent evidence of interference with wound healing. The same advantages in the irrigation of these patients were present as in the management of the closed transurethral procedures.

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CLINICAL USE OF CYTAL IN UROLOGY

T. L. SCHULTE, HOWARD J. HAMMER AND LLOYD R. REYNOLDS

Cytal* is a safe, nonhemolytic irrigating fluid which is helpful in the management of patients with transurethral prostatic surgery as well as patients managed transurethrally for tumor of the bladder. Originally Cytal was selected from a choice of 30 nonhemolytic solutions because of its optical superiority when viewed through the lens of the resectoscope. In testing this point, the various solutions were mixed with the proper concentration of the washings from irrigating fluid after transurethral resection where human blood was present in order to establish a controlled situation simulating conditions found in the operating room. Subsequently, it was noted that Cytal had an additional attribute in that it reduced the tendency of blood to form free clots in the bladder and to obstruct the irrigation catheter postoperatively.

In this study the solution diluted 1 part Cytal to 9 parts sterile water was used in transurethral resections, using both the direct vision Thompson resectoscope and the lens Stern-McCarthy resectoscope, in over 100 patients for a period of more than one year. The advantages of any nonhemolytic fluid most especially are at the conclusion of the operative procedure where most of the prostatic tissue has been removed down to or near the capsule and when a flow of irrigating fluid into the venous system might occur. It is in this type of case where the solution naturally has its greatest safety factor.

However, at this stage of the operative procedure there is another problem which deserves consideration. There usually forms, especially on the floor of the prostatic bed behind the verumontanum, extending from approximately 4 to 8 o'clock, a clot which results from venous ooze. As everyone knows, this clot is troublesome and must be scraped off with the loop before adequate fulguration and hemostasis are accomplished. Using water or other common irrigating fluids, the clot forms a hard mass on the loop of the resectoscope and must be removed. During the ensuing time more bleeding and more clot occur in the base. Therefore, much time is wasted with this procedure using water. However, while using Cytal, this clot is soft, readily washes away, and does not adhere to the loop; and at the bleeding point the venous ooze readily can be seen and fulgurated, actually saving time and preventing the necessity of removing the loop from the instrument and cleaning it.

In the transurethral management of bladder tumors it is well to consider using Cytal. Cutting deeply into the bladder wall, as one must do in order to prevent local recurrence at the site of the tumor, the same problem is presented as in doing a transurethral resection of the prostate when one resects deeply into the prostatic capsule where venous sinuses and large veins may be exposed to the

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Accepted for publication March 18, 1953.

* A solution, each 100 cc of which contains: Sorbitol 27.00 gm; Mannitol 5.40 gm; Methyl parahydroxybenzoate 5.0 mg; Propyl parahydroxybenzoate 1.0 mg; Butyl parahydroxybenzoate 1.0 mg.

irrigating fluid. It is in these patients that Cytal has a very definite safety factor. Again, as in the transurethral resection of the prostate, there may be a considerable amount of venous ooze at the base of the tumor site. Cytal facilitates determining the exact point of the bleeding.

After using Cytal as an irrigating solution in the transurethral management of prostatic resection and in the transurethral resection of bladder tumors, it occurred to us that it might be worth while to use this as a postoperative irrigating fluid. This has been done in over a hundred patients using the diluted solution as an irrigating medium rather than saline. It has also been used in concentrated form to prevent firm clots if bleeding becomes excessive.

The reason why we considered using Cytal as a postoperative irrigant after transurethral resection of the prostate or transurethral resection for bladder tumor was because we had the unfortunate experience of seeing three patients with masses of fibrin in the bladder. One of these was a woman 94 years of age who had had a resection for bladder tumor, was dismissed with clear urine, and during her course at home (she was ambulatory) developed some bleeding. She did not call our attention to this. Because of her age, her family did not seek further medical advice. The patient apparently continued to bleed slowly into the bladder. She subsequently developed bladder spasms and urinary incontinence and for this reason was hospitalized. At this time cystoscopy revealed a mass about the size of a tennis ball, grayish white, and almost cartilaginous in consistency, which required suprapubic cystotomy to remove this mass which proved to be fibrin (fig. 1).

In two subsequent patients who were irrigated with saline masses of fibrin developed in the bladder. These both required cystoscopy under anesthesia

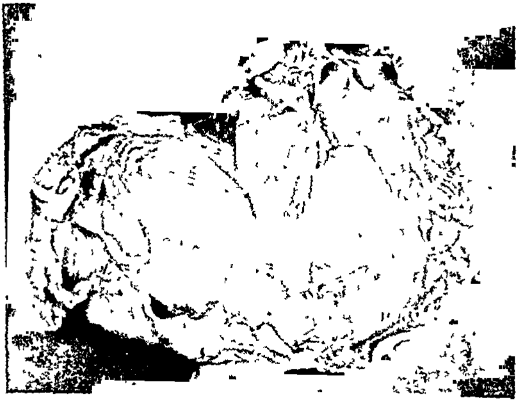

FIG 1 Cross section of fibrin clot removed from bladder. Color is greyish white; consistency that of benign adenomatous prostatic tissue.

and an actual resection of the clot using the direct vision Thompson resectoscope. In each case the clot was, as in the first patient, grayish white and firm, in consistency similar to the tissue of benign prostatic hypertrophy, and in each was about the size of a golf ball.

It occurred to us that perhaps irrigating with saline might be washing away the red blood cells but leaving fibrin to form a mass which could give subsequent difficulty. We have all had experience with the formation of a hard clot in the bladder following irrigation through a catheter postoperatively. Apparently the saline contributes to the firmness of the clot. The dark color is due to the hemoglobin. It was not until we observed these three patients cited, who had a grayish white fibrin clot of good size, that we became aware of its significance. We then realized that if, instead of using saline, we employed some other solution, one which would not so firmly precipitate the fibrin, we might avoid this difficulty.

Accordingly, Cytal solution was used to irrigate indwelling catheters postoperatively for transurethral resection of the prostate and of bladder tumors. It was found that whereas in using saline one was required to irrigate the catheter, for example every 15 minutes, using the diluted Cytal, one need irrigate the bladder only every hour to an hour and a half or even longer. It was found that with this solution the aspirated material returns a smoky red color rather than the usual red color as when saline is used. It is also free of any firm clots. Among patients who had postoperative bleeding after the catheter had been removed and had to be replaced, frequently clots were present in the bladder. A concentrated solution of Cytal softened these clots and made it possible to evacuate them completely; whereas, using saline, the clots would remain firm enough so that they would not come through a rubber catheter and would require an anesthetic and evacuation of the clots in the operating room. We consider this a distinct advantage from the standpoint of safety to the patient. We have, therefore, used this solution more or less routinely in the management of postoperative irrigation in the transurethral resection of the prostate and of transurethral resection for bladder tumors.

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In conclusion, therefore, we believe that Cytal is a safe solution which is non-irritating to tissues, does not interfere with wound healing, and does not cause prolonged postoperative bleeding In using the solution as a postoperative irrigant, it is not necessary to irrigate nearly as often as when using saline, and apparently there is no danger of the formation of a hard clot Naturally, arterial bleeding must be managed by electrocoagulation As far as venous ooze is concerned, this can be well managed using the Cytal solution which is a very definite adjunct in the management of patients with prostatic or bladder tumor surgery

909 Hyde St , San Francisco, Calif

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Ideal Bladder Substitution Justin J Cordonnier and (by invitation) Harvey Butcher, St Louis, Mo

Uretero Enterostomy, 'Combined' Technique Wyland F Leadbetter and (by invitation) Burdick G Clarke, Boston, Mass

Foley Y Plasty and Mechanism of Anomalous Vessel Obstruction Frederic E B Foley, St Paul, Minn

TUESDAY, JUNE 1

Motion Pictures, 8 00 to 9 00 a m

Cinefluorographic Studies of Bladder and Urethral Function in Human and Dog John A Benjamin, Rochester, N Y

Culp Pyeloplasty John K Lattimer, Archie Dean and (by invitation) Herman Wechsler, Roland Kohen and Jack Holden, New York, N Y

Ureteral Surgery Without Intubation Frank C Hamm, Brooklyn, N Y

Scientific Sessions

Permanent Diversion of the Urinary Stream John K deVries, East Orange, N J
Discussion Austin I Dodson, Sr , Richmond, Va

New Operation for Urinary Diversion Oswald S Lowsley and (by invitation) Thomas H Johnson, New York, N Y
Discussion James W Merricks, Chicago, Ill

'Combined' Uretero Enterostomy Technique Results After Four Years' Trial Wyland F Leadbetter, Boston, Mass
Discussion Justin J Cordonnier, St Louis, Mo

Squamous Epithelium of the Human Female Trigone, a Possible Explanation for Its Occurrence Charles Ney, New York, N Y
Discussion Rex E Van Duzen, Dallas, Texas

Cinefluorographic Studies of Bladder and Urethral Function John A Benjamin and (by invitation) Frederic T Joint, George H Ramsey, James S Watson and Sydney Weinberg, Rochester, N Y
Discussion Norborne B Powell, Houston Texas

Further Studies in Detection and Diagnosis of Prostatic Carcinoma J K Cline (by invitation), Birmingham, Ala

A Clinical, Cytological and Serological Approach to Early Detection of Cancer of the Prostate Gland A Preliminary Report Milton M Coplan, Frank M Woods, Perry D Melvin and (by invitation) S A Gunn and J E Ayre, Miami, Fla

Prospects for Earlier Diagnosis of Carcinoma of the Prostate Gland William F Boyer (by invitation), Tulsa, Okla
Discussions Herbert Brendler (by invitation), New York, N Y , William P Herbst, Sr , Washington, D C , John R Hand, Portland, Ore

WEDNESDAY, JUNE 2

Motion Pictures, 8:00 a m to 9 00 a m

Technique of Percutaneous Antegrade Pyelography and Trocar Nephrostomy Willard E Goodwin and (by invitation) William C Casey, Los Angeles, Calif

Transvesical Capsular Prostatic Adenectomy Jean Paul Bourque, Montreal, Canada

Transverse Incision for Suprapubic Prostatectomy Wyland F Leadbetter and (by invitation) Burdick G Clarke, Boston, Mass

Scientific Sessions

Advantages of the Transurethral Removal of Certain Bladder Tumors with a Report of Late Results in 400 Cases Gershom J Thompson, Rochester, Minn
Discussion Charles A W Uhle, Philadelphia, Pa

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PROGRAM, ANNUAL MEETING, AMERICAN UROLOGICAL ASSOCIATION, MAY 31–JUNE 1, 2, 3, 1954. WALDORF-ASTORIA, NEW YORK, N. Y.

MONDAY, MAY 31

Motion Pictures, 8:15 a.m. to 9:00 a.m.

PARASAGITTAL SECTION ANATOMY OF MALE PELVIS. Willard E. Goodwin and (by invitation) Joseph J. Kaufman, Los Angeles, Calif.

REPAIR OF VESICOVAGINAL FISTULA. James C. Sargent, Milwaukee, Wis.

OPERATION FOR CURE OF VESICOVAGINAL FISTULA. Vincent J. O'Conor and (by invitation) J. Kenneth Sokol, Chicago, Ill.

Scientific Sessions

LOWER URINARY TRACT IMPLANTS FROM CLEAR CELL CARCINOMA OF KIDNEY. John E. Heslin, William A. Milner and (by invitation) William B. Garlick, Albany, N. Y.
Discussion: Benjamin S. Abeshouse, Baltimore, Md.

MODIFICATION OF URINARY SURFACE TENSION BY ORAL GLUCURONIC ACID; its Application in Prophylaxis of Urinary Calculi. Harrison C. Harlin and (by invitation) Leon Wiesel, Brooklyn, N. Y.

ION BINDING PROPERTIES OF ELECTROPHORETICALLY SEPARABLE URINARY COLLOIDS IN HEALTH AND IN CALCULOUS DISEASE. Fred K. Garvey and (by invitation) William H. Boyce and Charles M. Norfleet, Jr., Winston-Salem, N. C.

DEMONSTRATION OF A COMMON BASIC MECHANISM IN EXPERIMENTAL RENAL CALCIFICATION PRODUCED BY VARIOUS ETIOLOGIC METHODS. Roger Baker and (by invitation) Francisco Sison, Washington, D. C.
Discussions: Edwin L. Prien, Brookline, Mass.; Howard I. Suby, Boston, Mass.; Rubin Flocks, Iowa City, Iowa

OBSERVATIONS ON HEALING OF URETERAL MUSCLE: Relationship to Intubation Ureterotomy. Jack Lapides and Eld[illegible] (by invitation), Ann Arbor, Mich.

EXPERIMENTAL STUDY OF URETERAL REPAIR IN DOGS BEARING UPON THE DAVIS INTUBATED URETEROTOMY. Saul Boyarsky and Oscar Duque (by invitation), Durham, N. C.
Discussions: Samuel A. Vest, Charlottesville, Va.; Edward W. Campbell, Philadelphia, Pa.

AORTOGRAPHY. J. Sydney Ritter, New York, N. Y.
Discussions: Parke G. Smith, Miami, Fla.; O. A. Nelson, Seattle, Wash.

SPECIAL PROBLEMS OF URINARY CONTROL IN PATIENTS WITH MULTIPLE SCLEROSIS. S. Richard Muellner, Boston, Mass
Discussion: R. Carl Bunts, Richmond, Va.

CLINICAL AND HISTOCHEMICAL STUDY OF ACID AND ALKALINE PHOSPHATASE IN NORMAL AND ABNORMAL PROSTATIC TISSUE (Third Prize, Essay Contest). John B. Goetsch (by invitation), New Haven, Conn.

Motion Pictures, 2:00 p.m. to 5:00 p.m.

THE COONEY-HORTON OPERATION FOR INCONTINENCE IN THE MALE. Frederick A. Lloyd, Chicago, Ill.

URINARY INCONTINENCE, SURGICAL TREATMENT. Albert Vergés-Fláque, New York, N. Y.

OPERATION FOR TOTAL URINARY INCONTINENCE. George H. Strong, Philadelphia, Pa. *and* (by invitation) Lt. Col. K. E. Van Buskirk, Washington, D. C.

NEW OPERATION FOR DIVERSION OF THE URINE WITH VOLUNTARY CONTROL OF FECES AND URINE. Oswald S. Lowsley and (by invitation) Thomas H. Johnson, New York, N. Y.

Treatment of Hypospadias. Donald R. Smith, San Francisco, Calif.

New Method for the Construction of the Urethra in Cases of Hypospadias. Victor F. Marshall and (by invitation) Robert M. Spellman, New York, N. Y.

The Pedicle Tube-Flap Method for Hypospadias. David M. Davis, Philadelphia, Pa.

Discussions: John N. Robinson, New York, N. Y.; Tracy O. Powell, Los Angeles, Calif.; Arthur B. Cecil, Los Angeles, Calif.

Experimental Use of Seromuscular Grafts in Bladder Reconstruction (Honorable Mention, Essay Contest). Horace D. Marucci and William C. Shoemaker (by invitation), Philadelphia, Pa.

Carcinoma of the Glans Penis. William J. Staubitz and Melbourne H. Lent (by invitation) and Oscar J. Oberkircher, Buffalo, N. Y.

Secondary Malignant Infiltration of the Penis; Report of Three Cases with Surgical Treatment. Frank C. Hamm and (by invitation) S. R. Weinberg, Brooklyn, N. Y.

Discussions: Archie L. Dean, New York, N. Y.; Chester A. Fort, Jr., Atlanta, Ga.

The Eleventh Rib, Subpleural, Approach to Kidney and Adrenal. Lorande M. Woodruff (by invitation), Brookline, Mass.

Discussion: George R. Nagamatsu, New York, N. Y.

PERCUTANEOUS ANTEGRADE PYELOGRAPHY AND HYDRONEPHROSIS (First Prize, Essay Contest). William C. Casey (by invitation) and Willard E. Goodwin, Los Angeles, Calif.

THE ROLE OF THE ADRENAL CORTEX IN PROSTATIC GROWTH. Pablo Morales and Herbert Brendler (by invitation) and Robert S. Hotchkiss, New York, N. Y.

Discussion: William Wallace Scott, Baltimore, Md.

RADICAL RETROPUBIC (SUPRAPUBIC) PROSTATECTOMY FOR CANCER. Richard Chute, Boston, Mass.

Discussion: Hugh J. Jewett, Baltimore, Md.

'SECONDARY' REGRESSION IN CARCINOMA OF PROSTATE AFTER ORCHIECTOMY. Vincent J. O'Conor and (by invitation) J. Kenneth Sokol, Chicago, Ill.

Discussion: Edwin P. Alyea, Durham, N. C.

PROGRESS IN PERINEAL PROSTATECTOMY: REPORT OF 2050 CONSECUTIVE PATIENTS. Leroy W. Lee and Edwin Davis, Omaha, Neb.

Discussion: William A. Barrett, Pittsburgh, Pa.

THE SEXUAL FUNCTION IN PARAPLEGIA. Herbert S. Talbot, West Roxbury, Mass.

Discussion: George C. Prather, Brookline, Mass.

MALIGNANT TESTICULAR TUMORS. Samuel L. Raines and (by invitation) Tom Hurdle, Memphis, Tenn.

CLASSIFICATION OF TUMORS OF THE TESTIS. Meyer M. Melicow, New York, N. Y.

Discussions: Lloyd G. Lewis, Washington, D. C.; Albert E. Bothe, Philadelphia, Pa.

PRESIDENTIAL ADDRESS: The American Urological Association; Reflections on the Past, Present and Future. J. A. Campbell Colston, Baltimore, Md.

THE RAMON GUITERAS LECTURE: CLINICAL AND LABORATORY RESEARCH CONCERNING MECHANISMS OF FORMATION AND CONTROL OF CALCULUS DISEASE OF THE KIDNEY. John Eager Howard, Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

THURSDAY, JUNE 3

Motion Pictures, 8:00 a.m. to 9:00 a.m.

RENAL BISECTION. George W. Slaughter, New York, N. Y.

INFRAPUBIC PROSTATECTOMY. J. Sydney Ritter, New York, N. Y.

RADICAL RETROPUBIC PROSTATECTOMY. Richard Chute, Boston, Mass.

Scientific Sessions

SYMPOSIUM: USE OF ANTIBIOTICS IN UROLOGY

TREATMENT OF NONSPECIFIC INFECTIONS. Wallace H. Herrell (by invitation), Lexington, Ky.

TREATMENT OF SPECIFIC INFECTIONS. John K. Lattimer, New York, N. Y.

TOXICITY FOLLOWING THERAPY WITH CARE OF THE PATIENT. Perrin H. Long (by invitation), New York, N. Y.

STERILITY IN WOMEN WITH ADRENOGENITAL SYNDROME TREATED BY ADRENALECTOMY AND BY CORTISONE. Seymour F. Wilhelm and (by invitation) Robert G. Marks, New York, N. Y.

Discussion: George F. Cahill, New York, N. Y.

THE INTUSSUSCEPTED ILEAL CYSTOSTOMY (Second Prize, Essay Contest). Gilbert I. Smith and Frank Hinman, Jr. (by invitation), Los Angeles, Calif.

A NEW DEVELOPMENT FOR LIGHTBEARING SURGICAL INSTRUMENTS. Henry Bodner, Los Angeles, Calif.

Discussion: J. Robert Rinker, Augusta, Ga.

Treatment of Hypospadias Donald R Smith, San Francisco Calif

New Method for the Construction of the Urethra in Cases of Hypospadias Victor L Marshall and (by invitation) Robert M Spellman, New York, N Y

The Pedicle Tube Flap Method for Hypospadias David M Davis, Philadelphia, Pa

Discussions John N Robinson, New York, N Y , Tracy O Powell, Los Angeles, Calif , Arthur B Cecil, Los Angeles, Calif

Experimental Use of Seromuscular Grafts in Bladder Reconstruction (Honorable Mention, Essay Contest) Horace D Marucci and William C Shoemaker (by invitation), Philadelphia, Pa

Carcinoma of the Glans Penis William J Staubitz and Melbourne H Lent (by invitation) and Oscar J Oberkircher, Buffalo, N Y

Secondary Malignant Infiltration of the Penis, Report of Three Cases with Surgical Treatment Frank C Hamm and (by invitation) S R Weinberg, Brooklyn N Y

Discussions Archie L Dean New York, N Y , Chester A Fort, Jr , Atlanta, Ga

The Eleventh Rib, Subpleural Approach to Kidney and Adrenal Lorande M Woodruff (by invitation), Brookline, Mass

Discussion George R Nagamatsu, New York, N Y

SCIENTIFIC EXHIBIT*

DR. SAMUEL A. VEST, *Chairman*

THE BIOCOLLOIDS OF URINE IN HEALTH AND IN CALCULOUS DISEASE. William H. Boyce (by invitation), Fred K. Garvey and (by invitation) Charles M. Norfleet, Jr., Winston-Salem, N. C.

EXPERIMENTS WITH FROZEN SPERMATOZOA. R. G. Bunge and (by invitation) J. K. Sherman, Iowa City, Iowa

RETROCAVAL URETER, NEW TECHNIQUE OF DIAGNOSIS AND TREATMENT. Donald A. Burke, William H. Muller (by invitation) and Willard E. Goodwin, Los Angeles, Calif.

TECHNIQUE OF RADICAL RETROPUBIC PROSTATECTOMY. Richard Chute, Boston, Mass.

PHOTOGRAPHIC HISTORY OF THE AMERICAN UROLOGICAL ASSOCIATION. Wirt B. Dakin, Los Angeles, Calif.

PERINEAL PROSTATECTOMY: RESULTS IN 2050 CONSECUTIVE PATIENTS. Edwin Davis and Leroy W. Lee, Omaha, Neb.

PERMANENT NEPHROSTOMY. John K. deVries, East Orange, N. J.

PERCUTANEOUS NEEDLE PUNCTURE ANTEGRADE PYELOGRAPHY AND TROCAR NEPHROSTOMY IN HYDRONEPHROSIS. Willard E. Goodwin and (by invitation) William C. Casey, Los *Angeles, Calif.*

THE INTUSSUSCEPTED ILEAL CYSTOSTOMY. Frank Hinman, Jr. and Gilbert I. Smith (by invitation), San Francisco, Calif.

CHEMOTHERAPY OF RENAL TUBERCULOSIS. John K. Lattimer and (by invitation) Roland Kohen and Louis L. Spivack, New York, N. Y.

URETERO-ENTEROSTOMY: 'COMBINED' TECHNIQUE AND RESULTS. Wyland F. Leadbetter and (by invitation) Burdick G. Clark, Boston, Mass.

A NEW ARTIFICIAL BLADDER OPERATION. Oswald S. Lowsley and (by invitation) Thomas H. Johnson, New York, N. Y.

ROENTGEN GRID THERAPY FOR ADVANCED CARCINOMA OF THE BLADDER. Hirsch Marks (by invitation), New York, N. Y.

CLASSIFICATION OF TUMORS OF THE TESTIS. Meyer M. Melicow, New York, N. Y.

PLASTIC TUBING IN PELVIOPLASTY. William L. McLaughlin, Hanover, N. H.

A UROLOGICAL OPERATING CRADLE. George R. Nagamatsu, New York, N. Y.

AORTOGRAPHY ASSOCIATED WITH RETROPERITONEAL PNEUMOGRAPHY AND PYELOGRAPHY. Alejandro Paloma and (by invitation) Eduardo Lizarralde A., Dagoberto Sosa M. and Estuardo Zirion, Guatemala, C. A.

POLYCYSTIC DISEASE OF THE KIDNEY. John F. Patton and (by invitation) Neal S. Bricker, Denver, Colo.

URINARY SURFACE TENSION, COLLOIDS AND CALCULI. R. A. Ravich and E. F. Revici (by invitation) and A. Ravich, Brooklyn, N. Y.

INFRAPUBIC PROSTATECTOMY. J. Sydney Ritter and (by invitation) A. A. Johnson and Henry Ritter, Jr., New York, N. Y.

RHABDOMYOSARCOMA OF THE BLADDER. Edgar A. Slotkin and (by invitation) Robert DeW. Davis, Buffalo, N. Y.

SURGICAL TREATMENT OF HYPOSPADIAS. Donald R. Smith, San Francisco, Calif.

URETEROPLASTIES. Albert Vergés-Flaqué, New York, N. Y.

STERILITY IN WOMEN WITH ADRENOGENITAL SYNDROME TREATED BY ADRENALECTOMY AND BY CORTISONE. Seymour F. Wilhelm and (by invitation) Robert G. Marks, New York, N. Y.

THE ELEVENTH RIB, SUBPLEURAL, APPROACH TO KIDNEY AND ADRENAL. Lorande M. Woodruff (by invitation), Boston, Mass.

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* The Scientific Exhibit has been erected under the supervision of the Director of Exhibits, Mr. William P. Didusch.

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Ambutainer Co , New York, N Y	58
American Cystoscope Makers, Inc , New York, N Y	38, 39, 40, 41, 42, 43, 49, 50, 51, 52, 53, 54, 55, 56
Astra Pharmaceutical Products, Inc , Worcester, Mass	26
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Northeastern Section—Chateau Frontenac, Quebec City, Quebec, Canada, September 19–22, 1954
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South Central Section—Colorado Springs, Colo., October 18–20, 1954

Members of executive committees of Sections, and officers and members of executive committees of Branch Societies are listed on pp. 982–984, December 1953 issue

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ESSENTIAL RENAL HEMATURIA

H EDWARD MACMAHON AND ROCCO LATORRACA

From the Department of Pathology, New England Medical Center, Boston, Mass

In the course of a routine examination of a kidney removed because of "essential hematuria," in which no gross lesion other than a small area of congestion at the fornix of one of the minor calyces was found, a chance histological section revealed a direct channel of communication between the lumen of a dilated venous sinus and the adjoining calyx The exact site of communication was at the fornix, where a narrow lumen, lined in part by endothelium and in part by transitional epithelium formed the connecting link There was no significant inflammatory reaction, no concretion, no tumor and no evidence of thrombosis This finding initiated a search for similar lesions in kidneys removed for unexplained hematuria

In the course of three months, two additional kidneys have been submitted to the laboratory for study, with the clinical diagnosis of "essential hematuria" Each of these was very carefully examined, and serial sections were cut from the region of the fornices In each of these kidneys a direct channel of communication between vein and calyx was found This finding of a very simple source of bleeding common to these three consecutive cases of "essential renal hematuria" is the basis for this report

For years the term "essential hematuria" has been used in the clinic and in the laboratory to designate cases of severe, recurrent, unilateral bleeding from the kidney in the absence of either an obvious source or mechanism of hemorrhage Palliative treatment has usually been unsatisfactory, and as a result nephrectomy has become the accepted form of therapy Although this has proven to be helpful to the patient, it has thrown little light on the nature of the underlying disease In few cases an obvious site of bleeding has been found by the pathologist, but with these few exceptions the kidney has failed to reveal its secret As a consequence there has grown up in the clinic an air of mysticism about this condition and in the laboratory, a sense of defeat

CASE REPORTS

Case 1 L W (Hospital No 142539 M H), a 51 year old man, for a period of 2 weeks had observed a progressive change in color of urine until it seemed that he was passing frank blood Cystoscopy revealed profuse bleeding from the right upper urinary tract Retrograde pyelography showed distorted filling of medial calyces of right kidney There was no definite evidence of tumor or concretion The ureter was normal Bleeding could not be controlled and nephrectomy was imperative The postoperative condition was good, and convalescence has been uneventful

This kidney (S 52 1947 M H) on gross examination was regular in size, shape and consistence The capsule stripped easily from a smooth cortex Petechial

Presented at a meeting of the New England Society of Pathologists May 19, 1953

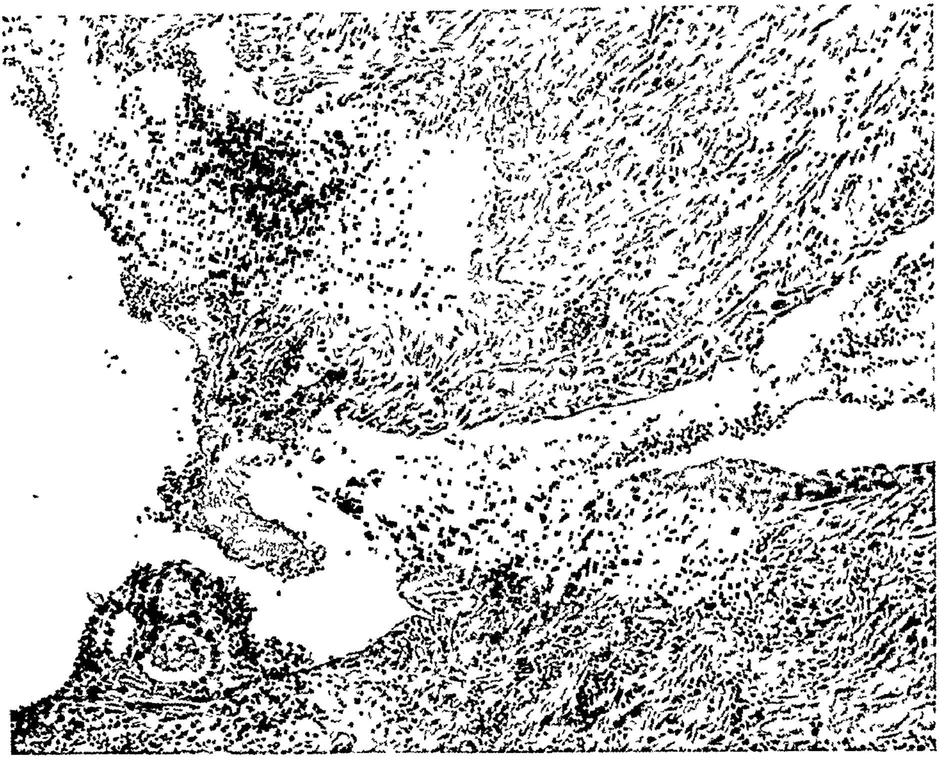

FIG. 1 (S-52-1947). Section of kidney showing exact point of communication between calyx on right and lumen of large gaping venous sinus on left. Channel uniting these two contains scattered red blood cells and little plasma. Lower surface of channel is partially lined by narrow layer of transitional epithelium continuous with mucosa of calyx on right. Opposing upper surface is lined by vascular endothelium which continues on left to line venous sinus. × 150

hemorrhages were found in the cortex, and there was fresh bleeding beneath the mucosa of much of the pelvis. There was no hydronephrosis, and a very careful examination for signs of inflammation or stone or tumor was fruitless. No source for the massive bleeding was found. Histological examination confirmed the small areas of bleeding into the cortex and into the loose tissues beneath the pelvic mucosa, but what proved to be much more important was the unexpected presence of a direct communicating channel between the lumen of a large thin-walled venous sinus and one of the calyces (fig. 1). The exact site of communication was at the fornix of the calyx. The calyx in this area was unusually long and narrow, while the nearby vessels were numerous, thin-walled and telangiectatic. The channel of communication was of particular interest in that one wall, in the plane in which the section was cut, was lined by transitional epithelium continuous with the visceral surface of the calyx, whereas the opposing surface was lined by the vascular endothelium of the involved vessel.

Case 2. F. H. (Hospital No. 74576 N.E.C.H.), a 56 year-old woman, complained of painless hematuria of three days' duration. The urine was bright red. There was no history of injury, but for one year the patient had noticed urgency of urination There was no frequency, nocturia or burning Urinalysis revealed 0 01 per cent albumin, specific gravity 1 025, and many red blood cells On cystoscopy, blood was seen flowing from left ureter, but a retrograde pyelogram on the left was read as negative This kidney was explored and nephrectomy was performed Convalescence was uneventful, and the urine has remained free of red blood cells

This kidney (S 53 297 N E M C) was quite regular in respect to size, shape, color and consistence Hemisection revealed a very small blood clot lightly adherent to the inner surface of one of the minor calyces Vessels throughout the peripelvic fat in the region of the hilus were congested A large block to include the entire calyx containing the blood clot was selected for examination, and serial sections were prepared for study Microscopic examination again revealed an open communication between the lumen of one of the large tributaries of the renal vein and the adjacent calyx As in the first case, the point of communication was at the fornix (fig 2) It is important to point out that this channel of communication was only seen in three consecutive sections of the many serial sections prepared from this area The wall of the venous sinus was represented by a single layer of endothelial cells There was no inflammatory reaction, nor was there any evidence of thrombosis The small blood clot that *was visible in the gross specimen was lightly attached to a small bare area of* the calyx immediately adjacent to the point of communication Sections from the remainder of the kidney were essentially free of disease

Case 3 V F (Hospital No 43062 M H), a white man, 24 years of age, was admitted complaining of eight days of painless gross hematuria There had been some vague discomfort in the lower back for a few days preceding the onset of hematuria, but there had been no injury The physical examination was essentially normal The blood pressure was 120/90 Urinalysis specific gravity 1 022, albumin 2 plus, many red blood cells, no casts Urea nitrogen 19 8 mg per cent Sedimentation rate 17 mm per hour Cystoscopy showed bleeding from the left ureteral orifice Retrograde and excretory pyelograms were reported as showing an irregular negative shadow within the lateral aspect of the left pelvis The kidney was explored, but the pelvis could not be adequately examined in situ, and to remove the source of bleeding, the kidney was excised Convalescence was uneventful, and hematuria ceased completely following the operation

This kidney (S 53 529 M H), with the exception of scattered punctate hemorrhages in the cortex and flame shaped hemorrhages beneath the mucosa of the pelvis, was considered healthy There was no recognizable area of inflammation, there was no tumor, and there were no concretions No satisfactory source of bleeding was found to explain the severe hematuria On the basis of earlier studies, *the calyces and their fornices were carefully examined, and* representative blocks from these areas were studied in step sections As in the case of the two kidneys already described, a direct channel of communication was identified linking one of the thin walled venous sinuses with one of the calyces in the region of the fornix (fig 3) The channel was partially lined on one side by

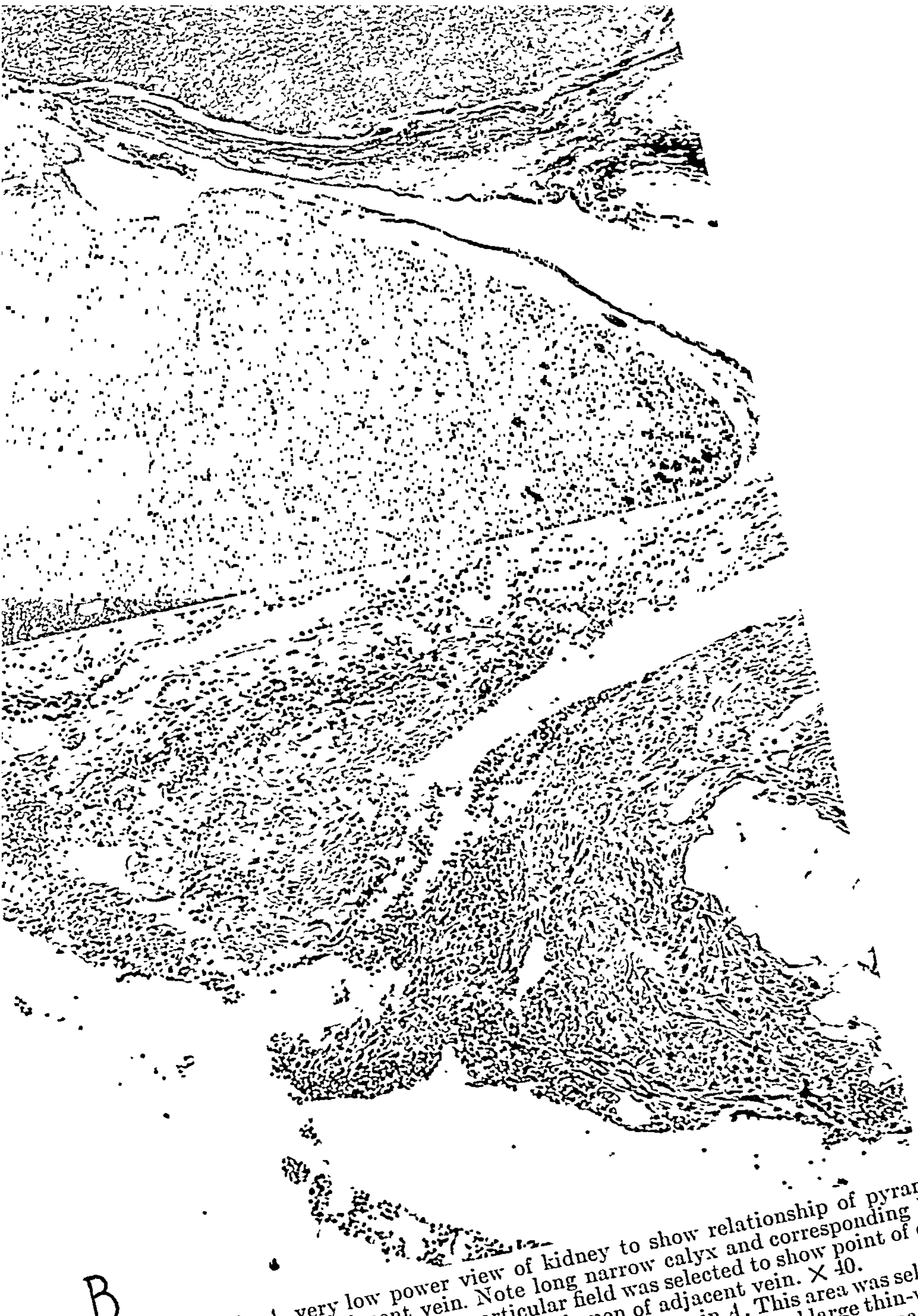

FIG. 2 (S-53-297). *A*, very low power view of kidney to show relationship of pyramid, calyx, fornix of calyx and adjacent vein. Note long narrow calyx and corresponding long thin-walled tributary of renal vein. This particular field was selected to show point of communication, at fornix of calyx, between calyx and lumen of adjacent vein. × 40.

B, higher power magnification of field in region of fornix seen in *A*. This area was selected to show exact site of communication between calyx above and to right, and large thin-walled venous sinus below and to left. Channel joining the two is freely patent but is partially filled with blood. × 150

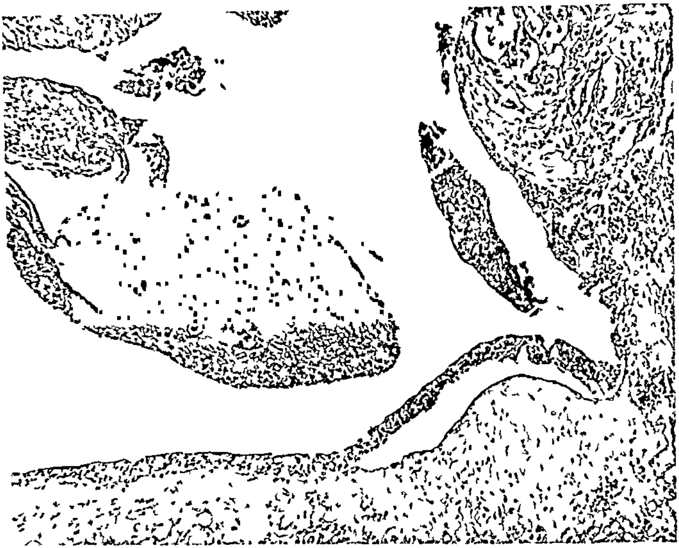

FIG 3 (S 53 529) Section of kidney in region of fornix of calyx This field was selected to show exact site of communication between venous sinus above and calyx below A small segment of transitional epithelium has become detached and lies freely in channel uniting vein and calyx Note that part of channel is lined by endothelial cells and part by transitional epithelium Above and to right, small cluster of epithelial cells is incarcerated in organizing fibrin × 45

transitional epithelium and on the other by vascular endothelium At one point there were signs of repair in which nests of epithelial cells were incarcerated in organizing granulation tissue, and the underlying wall showed a minimal resorptive inflammatory reaction

DISCUSSION

Most studies of the vascular bed of the human kidney have been focused on the arterial tree, the capillary tuft, the intertubular system of capillaries, and the debatable circulation of the pyramids Comparatively little attention has been given to the veins and their sinus like tributaries Perhaps this is because they are so inconspicuous in kidneys removed at operation or in others examined at the autopsy table It is generally known, of course, that the renal veins are relatively large, that they vary greatly from one patient to another, that their tributaries course anterior and posterior to the pelvis in the region of the hilus of the kidney, that anastomoses are common, particularly in the region of the base of the pyramids and that the left renal vein occasionally passes under the aorta instead of over it, but few realize how extraordinarily close these vessels may lie to the calyces Not infrequently they are incorporated in their walls What is equally important is that the tributaries of

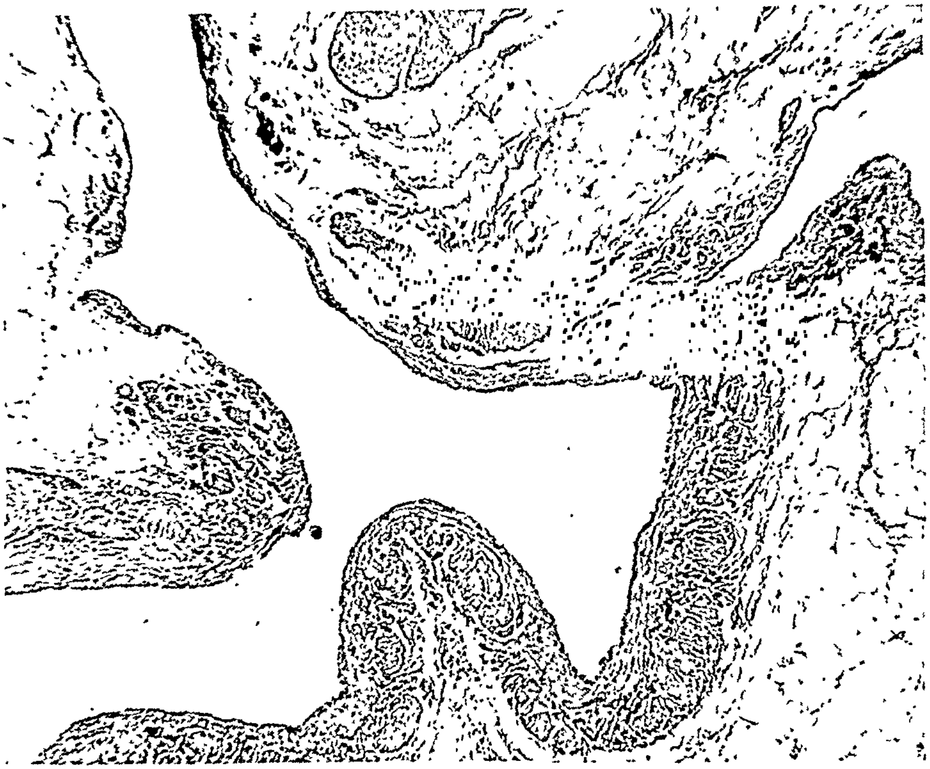

FIG. 4 (S-53-529). Section from hilus of kidney. This field was selected to show venous sinuses at right and left above, entering a medium vein. Note very thin wall of sinus in contrast to thick muscular wall of vein. Lumina of venous sinuses are often larger than veins into which they flow. Note particularly abrupt change in character of wall at point sinus enters vein. A well-defined ring of smooth muscle encircles sinus as it enters larger thick-walled vein. × 140

branches of the renal vein are often as large or larger than the veins into which they flow, that these sinus-like tributaries have extremely thin walls, that they possess no valves, and that as they enter the veins there may be a sudden and abrupt change in the character of the walls (fig. 4). These peculiarities in the renal veins favor the possibility of a direct communication occurring between vessel and calyx, and conversely between calyx and vessel, as seen by the roentgenologist in retrograde pyelograms and referred to as a "pyelovenous reflux."

Another territory within the kidney that has been neglected in routine gross and histological examinations of this organ is the area comprising the minor calyces and in particular, the region of the fornices. In the study of these three cases, the pathology in this area revealed the exact source of bleeding. Calyces vary considerably in size, in shape, in the structure of their walls and in the construction and shape of their fornices and especially in their relationships to veins and blood sinuses.

In these veins and calyces we have two variables, and it would seem that a particular combination of these could determine the possibility of establishing a direct communication from one to the other, abetted, of course, by the physiological variables of pressure within the calyces on the one hand and within the venous sinuses on the other In this way anatomical factors would largely determine the site of bleeding, whereas physiological variants could determine the actual mechanism Naturally, in the presence of a tumor, stone or inflammatory erosions, other factors could dominate the scene, but in the absence of these, simple anatomical relationships and physiological variants in pressure alone could initiate massive, recurrent hemorrhage One does not have to look beyond the anatomy of the calyx, fornix and adjacent areolar tissues and vessels to explain the occasional occurrence of a pyelovenous reflux in roentgenological visualization of the kidney, the extravasation of urine into the perihilar tissues with secondary inflammation, and the probable spread of infection locally from the pelvis into the peripelvic fat, and distally via the blood stream, from a septic focus within the kidney

An interesting feature of the three cases previously described was the comparatively short duration of the hematuria preceding nephrectomy This may explain the conspicuous absence of any severe or chronic inflammatory reaction or reparative process in the area of bleeding and may also account for the clarity with which these communicating channels could be demonstrated In chronic cases or in others in which there has been a long history of recurrent bleeding, one might expect signs of chronic inflammation and complex patterns of repair in the area of hemorrhage—and, unless the exact point of communication between vein and calyx was found, one could, as we have done in earlier studies, ascribe the bleeding to inflammatory reaction within the pelvic wall In other words, the mere presence of an inflammatory reaction or reparative process in or about the calyceal wall should not be an acceptable explanation for bleeding simply because nothing more was seen

Still other factors that may lead to confusion in cases of this type are the small areas of fresh bleeding that one so frequently finds beneath the mucosa of the pelvis, in the pyramids and in the substance of the cortex of kidneys that are removed at operation Little or no attention is paid to these in cases of hematuria in which there is an obvious condition such as tumor, stone or tuberculosis, but in other cases in which no gross lesion is visible, one grasps eagerly at every petechial hemorrhage to explain "the cause of bleeding" We admit that where there is free blood there may be a possible source of hematuria, but in cases in which there has been severe and recurrent bleeding from the kidney, one should find the exact source of bleeding, and by this is meant the point of communication between a vessel and the urinary tract, before discussing etiological mechanisms Actually, the severe form of bleeding seen in most cases of essential hematuria is not likely to have its origin in capillaries, or its mechanism one of simple diapedesis, but rather in larger vessels in which there has been a frank rupture Even when tumors or stones are found in association with massive renal hemorrhage, far too little attention has been given to the exact site or mechanism of bleeding It is our impression that the peculiarities of the tributaries of the renal veins both within the kidney parenchyma, and in the areolar tissue adjacent to the calyces, play a very important role in most cases of severe renal hemorrhage irrespective of the type of pathology found within this organ.

LITERATURE

Our finding in these 3 cases, of a direct channel of communication between vein and pelvis is not an original observation, nor is the emphasis that we have placed on the importance of the pericalyceal veins in spontaneous bleeding from the kidney ours alone, but what we would like to emphasize at this point is a fact that we believe has not been significantly appreciated, namely, that a more careful search in the region of the fornices may reveal the source of bleeding far more often than is generally found. Fuchs[1] in 1925 carefully described the very close relationship that exists between the tributaries of the renal veins and the mucosa of the fornix. He also pointed out how much more numerous the veins are in this area than the arteries, and though he had not seen a case, he postulated that in cases of "essential hematuria," a careful search of the veins adjacent to the fornix would some day reveal the source of bleeding. He also was able to show that by increasing the peripelvic pressure, the interlobar veins are compressed, leading to stasis and varix formation distal to the point of compression. Dalakapoulos[2] in 1937 gathered together a group of cases in which hemangiomas had been found in cortex, pyramids, pelvis and ureter in association with severe hematuria, and in reviewing the literature relating to hemangiomatous lesions of the kidney, referred to papers by Fenwick, Kidd, Jenkins, Wheeler and Schneider, in which angiomatous formations had been found either in the tips of the papillae or beneath the pelvic mucosa, but in none of these was an actual site of bleeding demonstrated. Meade[3] (1938) reported a single case in which a heminephrectomy was performed for unexplained uncontrollable bleeding from one of two pelves. In this case the vessels were described as large and dilated, showing in one area a minute angioma. The site of bleeding was not found, but it was inferred that there probably had been a rupture of a dilated vessel on the surface of the pyramid. Corbett[4] (1939) reported 4 cases of unilateral renal bleeding without clinical evidence of disease or abnormality of the kidney in which, following nephrectomy, two proved to be early cases of carcinoma, and the remaining two showed a low-grade inflammatory reaction. He mentions dilated vessels, but in none of the 4 cases was a direct site of bleeding demonstrated. Swinney[5] (1939) facetiously refers to the "essential hematuria" as a form of bleeding from the kidney in which there has been no clinically demonstrable cause, and then goes on to say that hemorrhage from a normal kidney does not occur. This paper is based on the report of 2 cases, in one of which a small hemangioma was found in one

[1] Fuchs, Felix: Untersuchungen über die innere Topographie der Niere. Ztschr. f. urol. Chir., **18:** 164, 1925.

[2] Dalakapoulos, N.: Nierenhämangiome. Ztschr. f. urol., **31:** 458, 1937.

[3] Meade, H.: A case of heminephrectomy for hematuria. Brit. J. Urol. **4:** 161, 1938.

[4] Corbett, D. G.: Unilateral renal bleeding without clinical evidence of disease or abnormalitv. J. Urol., **42:** 1179, 1939.

[5] Swinney, John: Some aspects of the pathology of essential hematuria. The Newcastle Med. J., **19:** 51 1939.

of the pyramids, while in the other a small hemangiomatous nodule projected from the mucosal surface of the pelvis. Riley and Swan[6] (1941) reviewed the literature of angiomas of the kidney and stated that not a single angioma had been found in the kidneys of 13,219 autopsies done at the Boston City Hospital. In this paper they describe a single case of their own and point out, as others had done before them, the problems in terminology in distinguishing true vascular tumors from collections of telangiectatic vessels in and outside the kidney. Johnson and Warwick[7] (1941) in a paper dealing with "essential hematuria" described 2 cases of mild recurrent hematuria in which angiomas of the pelvis were found, and go on to say that small angiomas may be the "cause of essential hematuria". Bobbitt et al.[8] (1944) described 2 cases of recurrent painless hematuria in which they found dilated veins in the papillae and assumed that the source of bleeding in essential hematuria was undoubtedly due to vessels rupturing into calyces. Rottino and Mohan[9] (1944) in a paper dealing with obscure causes of hematuria describe 3 cases in which hemangiomas were found in the kidney. In the first an area of ulceration could be traced from the surface of a pyramid into an underlying cavernous hemangioma. In the second case there was a double ureter and a double pelvis and many widely dilated blood vessels were found beneath the mucosa of the pelvis. The third case was from a 61-year-old man who had experienced intermittent bouts of hematuria for 36 years. At autopsy a large pyonephrotic kidney was found. The kidney parenchyma was reduced to a thin shell and scattered cauliflower hemangiomas were found over the surface of the pelvis. More recently McKay and others[10] reported two unusual causes of renal hematuria. In one patient they believed they could trace the source of bleeding to a ruptured dilated vein in the tip of one pyramid. In the second case they attributed the bleeding to capillaries in an area of papillitis. In all of these reports attention has been directed at the blood vessels, but with the possible exception of one, no direct channel of communication was demonstrated, nor was there any uniformity in respect to the type or location of the lesions described.

THERAPY

The problem of treatment in "essential hematuria" may be quite as difficult as is the search for the site of the hemorrhage, because to temporize may prove fatal, and so nephrectomy has become the final common denominator as therapy. This, however, is a radical procedure and may seem hardly justified in cases in which the kidney is otherwise normal. Unfortunately there has been no agreement on the location or mechanism of bleeding, and many cases, even after careful histological examination are still being reported as "site and mechanism of bleeding not found." Certainly the finding of a similar lesion, in a similar site, in three successive kidneys showing no other evidence of disease does not warrant considering this the only site or the only lesion that may be found—but it does warrant considering such a possibility and should initiate a more careful search of this area, with particular emphasis on the tributaries of the renal vein. It is of interest that among the palliative forms of therapy two have frequently been reported as giving some degree of relief. One of these is bed rest and the other decapsulation of the kidney—in either case a lowering of venous pressure within the kidney would seem the natural result. Yet, if there is a direct channel of communication between vein and pelvis, such forms of therapy are not realistic and experience has shown this to be the case. As long as one has no idea of the possibilities that are likely to exist in the kidney in cases of essential hematuria, nephrectomy would seem to be the therapy of choice, but if the lesion that we have demonstrated in these three successive kidneys should prove to be a common finding in "essential hematuria" then it does not seem beyond the realm of modern surgery to devise a method to treat the lesion and possibly save the kidney.

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[6] Riley, A. and Swan, W. J.: Angioma of the kidney. Urol. & Cutan. Rev., **45**: 377, 1941.

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[9] Rottino, Antonio and Mohan, Herbert: Renal hemangioma. An obscure cause of hematuria. J. Urol., **51**: 601, 1944.

[10] McKay, H. W., Baird, H. H. and Lynch, K. M.: Two unusual causes of renal hematuria. J. Urol., **61**: 1, 1949.

SUMMARY

Three cases of so-called "essential hematuria" are reported in which a single lesion, manifesting itself as a direct channel of communication between the pericalyceal venous plexus and the lumen of the calyx was demonstrated as the exact site of bleeding. Emphasis is placed on the importance of the venous plexus in severe bleeding from the kidney, not only in cases of "essential hematuria," but also in the presence of other kidney lesions. The literature is reviewed with particular emphasis on the so-called angiomatous and telangiectatic vascular lesions of the kidney. Finally in considering the problem of therapy, one is urged to be realistic and to consider the most probable type of lesion that may be found and to give more attention to the repair or removal of this lesion in an effort to save the entire organ.

The authors wish to thank Dr. Michael MacKenzie, pathologist to the Malden Hospital and Dr. Jacob Dyckman, pathologist to the Miriam Hospital in Providence for permission to study two of the kidneys included in this report.

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BILATERAL CARCINOMA IN POLYCYSTIC RENAL DISEASE—AN UNIQUE CASE

CAPT ANTHONY A BORSKI (MC USA) AND COL JAMES C KIMBROUGH (MC, USA)

From the Urology Service, Walter Reed Army Hospital, Washington, D C

A review of the literature fails to reveal any reported cases of bilateral renal carcinoma in polycystic renal disease The occurrence of unilateral renal carcinoma in polycystic disease, however was reviewed in 1940 by Melicow and Gile[1] and in 1952 by Johnson[2] and nine such cases were found The following is believed to be the only known case of bilateral renal carcinoma in polycystic renal disease to be reported to date

A 38 year old white man was admitted to Walter Reed Army Hospital on March 17, 1948 with intermittent headaches of 2 years' duration and a painless mass in the right flank In 1946 a routine physical examination revealed hypertension and a mass in the right flank, but there were no investigative studies made at that time The headaches had been increasing in intensity and were usually worse in the morning and subsided somewhat during the day There was no eye, ear, nose or throat disease to account for these headaches and the mass in the right flank caused no symptoms The patient was admitted to the Urology Service for study of the right flank mass Family history was pertinent in that one sister had a thyroid tumor and another sister and one nephew were known to have brain tumors There was no family history of polycystic renal disease

Physical examination showed the patient to be well developed, well nourished and in no distress His weight was 174 pounds and his blood pressure 140/90 The entire physical examination was within normal limits except that both kidneys were enlarged to palpation and the right kidney was larger and more irregular than the left The impression was that the patient had polycystic disease of the kidneys

Laboratory studies showed the following Blood urea nitrogen 15 8, urea clearance, 89 per cent, urine concentration, 1 022, CO_2 volume per cent, 56 2 (normal 53–72), total protein, 6 8 per cent, AG ratio, 3 2 Chest x ray was normal Excretory urogram showed enlarged kidneys with some distortion of calyces, especially the right inferior calyx, but the typical spidering effect of polycystic kidneys was not present

On March 30, the right kidney was explored It was noted that the lower pole was a solid mass of tissue There were many cysts present throughout the kidney and there was a multicystic surface Several large cysts were unroofed and others were aspirated A frozen section of tissue was reported as being doubtful At this stage of surgery, the patient was doing poorly, and in view of the fact that no positive diagnosis was made other than that of polycystic kidney the operation was completed Permanent sections of biopsy material showed adenocarcinoma, therefore, a right nephrectomy was performed on April 5 (figs 1 and

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[1] Melicow M M and Gile Harold J Urol , 43 767–773 1940
[2] Johnson W F J Urol 69 10 12 1953

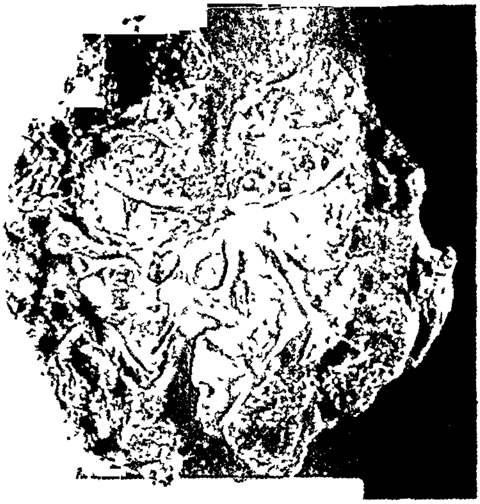

FIG. 1. Right kidney showing multiple cysts and multinodular tumor masses.

2, *A*). Radiation therapy to the right flank was started. On April 20, the patient noticed an unsteady gait and severe headaches but without visual disturbances. An electro-encephalogram was reported as being normal. Eye, ear, nose and throat consultation was negative. During the next 3 months there were no marked changes. In August vomiting of a nonprojectile type developed and without nausea. The electro-encephalogram was repeated and revealed left side amplitude asymmetry which was considered evidence of metastatic carcinoma. A neurosurgical consultant advised against exploration and, therefore, radiation to the brain was begun on September 10. The symptoms abated, but in November, headaches and vomiting recurred and radiation was once again started. Blood pressure at this time was 220/120. Spinal tap on December 14 revealed pressure 260 mm. water and protein, 154 mg./100 cc. On December 21 his blood pressure was 140/100. He received a total of 4800 roentgens through three different portals to the brain. In January 1949, he was asymptomatic and all studies were within normal limits except for the large left kidney which showed distortion of calyces. Typical spidering was not noted. The patient was discharged to outpatient care.

Second admission: The patient was again admitted to Walter Reed Army Hospital on June 19, 1951, for surgical treatment of the mass in the left flank. In the course of follow-up care, the left kidney was found to have at least one large cyst and several smaller ones. The patient was asymptomatic except for occasional right flank pain.

Physical examination showed the blood pressure to be 172/110. There was a 15 by 15 by 15 cm. mass in the left flank which was irregular, nontender, and which moved with respirations. The remainder of the physical examination was essentially negative.

Laboratory studies showed both the admission urinalysis and complete blood count to be normal. The phenolsulfonphthalein test revealed a 49 per cent excretion in 60 minutes. On June 26, a urinalysis showed 3 plus albumin; blood urea nitrogen, 26. Skeletal and chest x-rays were negative. An excretory urogram re-

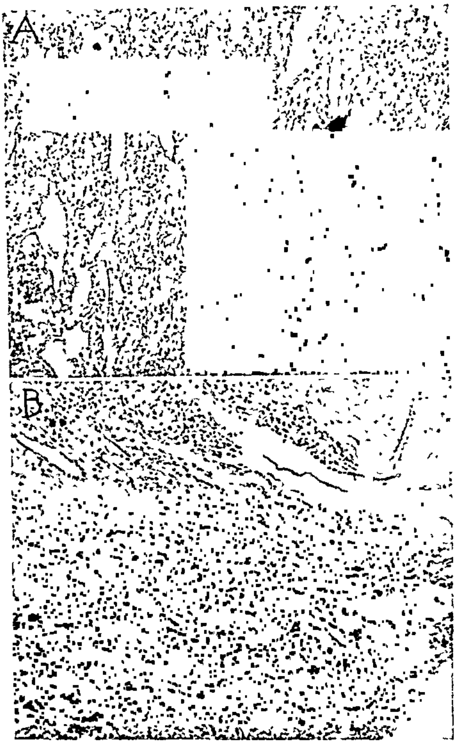

Fig. 2. *A*, low power section of right kidney showing adenocarcinoma. *B*, low power section of left kidney showing adenocarcinoma.

vealed an absence of the right renal shadow and fractional visualization of the left kidney.

On June 21, 1951, the left kidney was explored and many cysts were punctured. There were some firm areas which were suggestive of tumor and a biopsy specimen was taken. The postoperative course was uneventful. The pathological diagnosis was that of clear cell carcinoma of the kidney (fig. 2, *B*). The patient was started on radiation therapy to the left kidney. The amount of radiation received was 5688 roentgens through three portals to the left kidney.

Third admission: On December 8, 1952, the patient was again admitted to the hospital with intermittent chills and fever of 3 days' duration. He had also had severe intermittent left lumbar pains for several months. Three days prior to admission he had a fever of 103F with profuse night sweats. There were no urinary symptoms.

A physical examination revealed the patient to be well developed, but with an appearance of being older than his 43 years. Blood pressure was 160/95; temperature, 102F. He had slight abdominal tenderness and there was a large mass in the left flank which was slightly tender.

Laboratory studies showed the admission urinalysis to have a 1 plus albumin and a specific gravity of 1.016. The white blood count was 5,500. Urine culture revealed Escherichia coli and Streptococcus fecalis. The blood urea nitrogen was normal. Skeletal survey and chest x-rays were also normal.

An excretory urogram failed to reveal any visualization of dye. Phenolsulfonphthalein test showed 28 per cent excretion in 30 minutes. The patient was treated with streptomycin and penicillin and in 48 hours he was asymptomatic. Because of polycystic disease and carcinoma in the remaining kidney, no further diagnostic tests were performed. He was discharged on December 17, 1952, to be followed in the Outpatient Service.

DISCUSSION

The congenital nature of polycystic disease of the kidneys is undisputed. Pathogenesis is unknown and many theories have been advanced as to the etiology, but the most widely accepted theory is that of Hildebrandt.[3] The disease results as a failure of union between metanephroblastemic elements and the collecting tubules originating in its metanephric duct. Cystic formation results from blockage of glomerular secretion.

Nodular cystic enlargement of the kidneys is predominately bilateral. In cases thought to be unilateral, histologic study will almost always disclose this anomalous development in the opposite kidney.

When the renal cysts enlarge, they cause compression atrophy of the renal parenchyma and consequently renal failure ensues.[4]

There is no known causal relationship between polycystic disease and carcinoma of the kidney. Simultaneous occurrence of these conditions is considered to be a coincidence. The prognosis of polycystic disease is especially poor when the disease is recognized in childhood and is also poor in adults, although some patients live to an old age. When one kidney is removed, survival is not likely for more than a year or two, although survival for longer periods has been reported. Treatment of uncomplicated cases is fundamentally the same as for nephritis. Hematuria may demand nephrectomy if conservative measures fail to stop the bleeding.

Rovsing[5] has relieved pain in some cases and also has improved renal function by cyst puncture. Goldstein[6] has used cyst puncture and marsupialization of the kidneys to the wound. In this manner the cysts could continue to be aspirated postoperatively. Young employed aspiration and injections of 5 per cent sodium morrhuate solution and Fish[7] injected 50 per cent dextose solution.

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[3] Campbell, Meredith: Clinical Pediatric Urology: Philadelphia: W. B. Saunders Co., 1951.

[4] Bobbitt, R. M.: J. Urol., 50: 131-140, 1943.

[5] Rovsing, T.: Am. J. Urol. 8: 120-124, 1912.

[6] Goldstein, A. E.: J. Urol., 34: 536-547, 1935.

[7] Cahill, G. F. and Fish, G. W.: Trans. Am. Assoc. Genito-Urin. Surg., 38: 81, 1941.

Acute symptoms may be relieved and adequate drainage maintained by occasional careful dilatation of the ureters and renal pelvic lavage. Death is almost always due to uremia.

SUMMARY

A case of bilateral carcinoma in polycystic kidneys is presented. Despite the extremely poor prognosis, the patient has survived 5 years and is asymptomatic at the present time. A review of the literature fails to disclose any similar case.

ADDENDUM

The patient was re-admitted on December 15, 1953 complaining of nausea and vomiting, constant occipital headache, and difficulty in maintaining his equilibrium.

A physical examination revealed abnormal bilateral deep tendon reflexes, more pronounced on the left side. His blood pressure was 240/140 and there was a firm, nontender, fixed 20 cm. mass in the left upper quadrant. The electroencephalogram revealed an abnormal record with a slow wave focus in the left parieto-occipital area.

There was nothing unusual in the laboratory data except that the blood urea nitrogen determination was 27 mg. per cent.

The patient was given 1,942 roentgens to the occipital lobes, but the headaches persisted throughout the course of therapy. On February 7, he had a severe occipital headache and died shortly thereafter.

Several tumor areas in the polycystic left kidney were found at autopsy and an examination of the brain showed a 2 cm. tumor nodule in the cerebellum which had ruptured into the fourth ventricle. There was also a cyst in the cerebellum which was filled with old blood and necrosis. This cystic region, the pathologist felt, probably represented the cerebral metastases which had been destroyed several years earlier by previous radiation therapy.

Pathological diagnosis: Cerebral metastases, secondary to adenocarcinoma of the polycystic kidney.

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SURFACE SPREAD OF CARCINOMA: REPORT OF TWO CASES IN RENAL PELVIC TUMORS

JAMES R. LISA AND JOSEPH D. GIOIA

From Doctors Hospital, New York, N. Y.

The noninvasive spread of carcinoma along an epithelial surface may be extraordinarily extensive. The macroscopic changes are frequently minimal and can easily be overlooked. The importance of this method of spread in relation to surgical procedures is obvious. Recently there was encountered, in an extirpated kidney, an example of this method of tumor spread. A similar case was seen by one of us (J. R. L.) at French Hospital in 1944. These two cases form the basis of this report. Both were cases of squamous cell carcinoma of the renal pelvis.

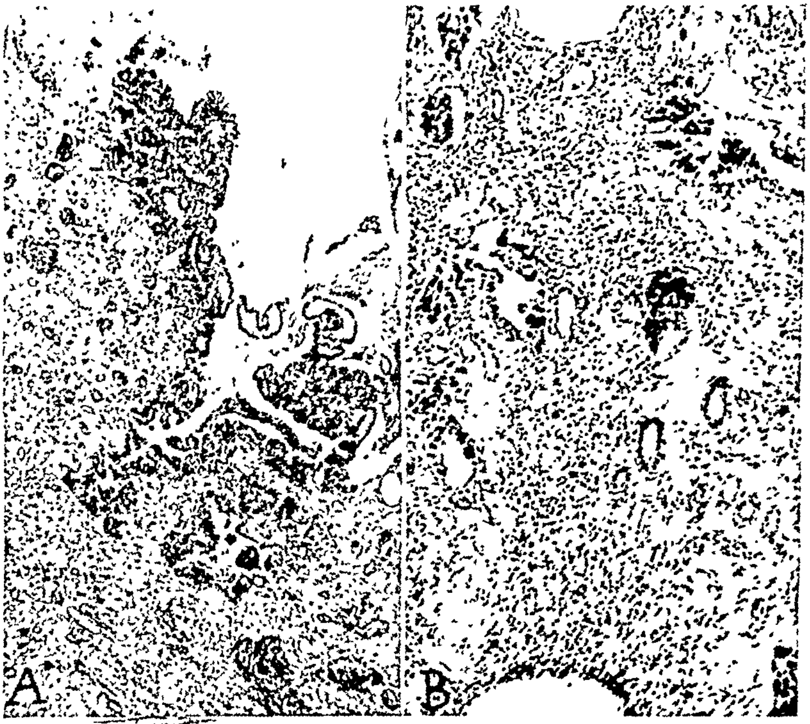

FIG. 1. Case 1. *A*, papillomatous carcinoma involves tip of renal papilla. Local surface spread and extension into tubules of medulla. *B*, tubular involvement higher in medulla extends to corticomedullary boundary.

The patients were men, 56 and 77 years of age respectively. The symptoms were those usually encountered in tuberculosis or malignancy. In case 1, the diagnosis of tuberculosis could not be confirmed by laboratory investigations. In case 2, a Papanicolaou preparation was positive for malignancy.

In case 1, a papilla in an upper calyx had a small eroded area, suggestive of a tuberculous lesion; the remainder of the pelvis and the renal parenchyma showed

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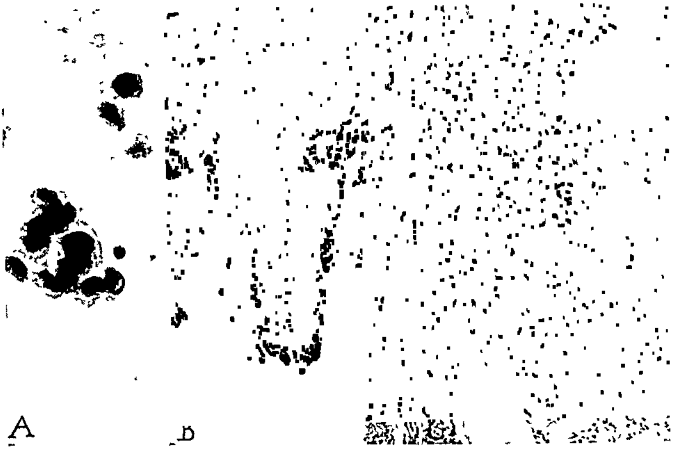

FIG. 2. Case 2. *A*, Papanicolaou preparation of urine shows presence of malignant cells. *B*, papillary carcinoma arises from pailla and cells spread over surface of pelvis. *C*, tubules in cortex are lined by malignant cells.

nothing else of note. In case 2, the kidney and about half the ureter were removed. A papilla of the lower pole was replaced by a white granular lesion measuring 7 by 6 cm. The remainder of the mucosa of the calyces, pelvis and ureter appeared edematous, soft and light gray-yellow in color.

The microscopic findings in each kidney had many features in common and will be described together (figs. 1 and 2). The local lesion at the papillary tip was papillomatous and the epithelial cells were neoplastic, non-keratinizing squamous in nature, showing anisocytosis, macronuclei, macronucleoli and hyperchromatism. The spread of the tumor over the mucosal surface of the pelvis was confined by the basement membrane and remained noninvasive. In case 1 it was limited to the neighborhood. In case 2 it had completely replaced the pelvic mucosa and spread down the ureter to the point of resection.

The parenchymal involvement was similar in nature to the pelvic. The tubular epithelium was replaced by tumor cells extending upward from the papillae. In case 1 it was local and penetrated to the corticomedullary boundary line. The parenchymal penetration in case 2 was much wider. The tumor penetrated to the capsule and most parts of the organ were involved.

Thanks are due to Dr. W. W. Brandes, Roosevelt Hospital, for the loan of the Papanicolaou preparation.

Poughkeepsie, N. Y. (*J. D. G.*)

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HISTOPATHOLOGY IN PROGNOSIS OF KIDNEY TUMORS

WILLIAM A. BARRETT AND EDWARD J. McCAGUE

From the Division of Urology, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pa.

This analysis deals with 210 cases of kidney tumors taken from the medical records of two large general hospitals, the Mercy and the Western Pennsylvania, in Pittsburgh, between January 1, 1933, and December 31, 1952. Their total admissions for this period were 281,099 and 249,053 for a grand total of 530,152. This represents one tumor case in every 1,525 admissions.

They have been reviewed primarily from the histological appearance of the tumor in an effort to determine what, if any, prognosis might be given from the microscopic picture. Out of the total of 210 cases so catalogued, eleven had to be eliminated because of the lack of sufficient evidence to indicate the correctness of the diagnosis. Of the remaining 199 cases, in which the diagnosis was certain, 157 were nephrectomized, had a biopsy, or a postmortem examination. These were the basis of the histological examination upon which this study was made.

Several surgeons, including general surgeons, were the operators in the cases studied. This, we believe, gives a general cross section of the treatment and results obtained. A complete study including histological examination of the tissue could not be made in some instances because of the great debilitation of the patient, the obvious extensive metastases, poor function in the opposite kidney, because the patient refused surgery or because, in some instances, the extent of involvement did not seem to warrant surgery. In such instances x-ray therapy was at times given.

In some instances the patients died after leaving the hospital without any definite word being received at the hospital, changed their family physicians or for various other reasons all trace of them was lost. Under such circumstances, the period of survival could not be determined, and in these instances the patients were considered dead unless they could be traced.

All of the histological slides of the remaining 157 cases were then studied without knowing the period of survival of the individual cases. Not wishing to rely solely on our own knowledge of histological pathology, we asked Dr. Howard H. Permar and Dr. Richard G. McMannus, pathologists at the Mercy and Western Pennsylvania Hospitals, respectively, to review these sections with us. Excepting cases of sarcoma, transitional cell and anaplastic or rapidly growing undifferentiated adenocarcinomas, our estimate of 5-year survivals was too often wrong.

The symptoms of which these patients complained had been present from 2 days to 2 years and the majority did not seek help until more than 2 weeks had passed. The greatest number presented themselves between 2 and 6 months after the onset of the symptoms. One or more of the familiar triad—hematuria, pain and tumor, were present in every instance. One hundred and five had

Read at annual meeting, American Urological Association, St. Louis, Mo. May 14, 1953.

TABLE 1. *Survival following treatment*

	NO	5 YEARS		10 YEAR +	
		No	Per cent cases operated	No.	Per cent cases operated
No treatment	44				
Radiation therapy only	27	2		1	
Biopsy only	13	0			
Biopsy plus x-ray therapy	6	0			
Exploration only	7	0			
Nephrectomy* only	69	9	8.8	7	6.8
Nephrectomy plus x-ray therapy	33	11	10.7	6	5.8
Totals	199	22	19 6	14	12.7

Cases treated since Jan 1, 1948 have not been considered regarding 5 year survival —43 cases.

* 1 patient nephrectomized in 1928 is still well.

hematuria; one hundred and three, pain; and fifty-five complained of a tumor. The complaint least often mentioned was weakness or symptoms referable to some area of metastasis.

Symptoms referrable to other organs were at times the means of diagnosing the primary tumor. Four patients had undergone brain operations and two had lung operations for the removal of what proved to be a metastatic lesion. Two patients had pathological fractures of the leg and one had a tumor in the muscle of the leg. A total of 11 patients had clinical evidence of brain metastasis and seven had generalized metastases at the time of admission to the hospital. In 6 instances superficial lymph nodes were removed as a means of diagnosing the primary tumor.

Table 1 shows the survival following treatment with particular reference to the 5 and 10-year periods. The total number of tumors analysed was 200. In 69 cases, nephrectomy alone was done, nine or 8.8 per cent of which survived a period of 5 years and of these seven or 6.8 per cent survived a period of 10 years. One patient, who was operated on in 1928 and does not belong in this series, is still well In 33 instances, nephrectomy plus x-ray therapy was given. Eleven or 10.7 per cent of these survived a period of 5 years and six or 5.8 per cent survived a period of 10 years. This is a 19.6 per cent survival for 5 years of those nephrectomized. In this analysis, the cases treated since January 1, 1948 have not been considered in regard to these survival periods. There were 43 cases of kidney tumors treated between the years 1948 and 1952 inclusive.

Table 2 indicates to us what we consider a rather startling fact, namely, out of 199 cases, one hundred and one were definitely known to be dead at the end of the first year; sixty-four were definitely known to be alive; and, thirty-four were not reported so their fate could not be determined.

Figure 1 indicates the cases surviving for the various numbers of years.

In the discussion of these tumor cases we have made no attempt to classify them beyond:

TABLE 2. *Results at end of first year*

	NO.	PER CENT
Living	64	32.1
Dead	101	50.7
Unreported	34	17.0

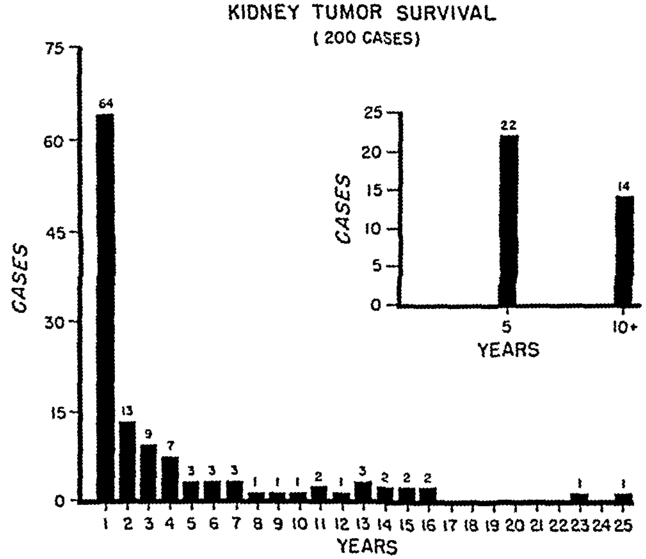

FIG. 1. Showing number of patients who have survived for years indicated. Smaller graph depicts number of those surviving 5 years or longer and number surviving 10 years or more.

1. Adenocarcinoma (fig. 2), all tumors arising from the parenchyma, which includes all hypernephromas or Grawitz tumors, renal cell carcinoma, papillary adenocarcinoma, tubular cell tumors, cystic and papillary tumors, granular celled and clear celled tumors. These are generally considered to have been derived from the mesodermal renal cap.

2. Transitional cell tumors (fig. 3), all tumors which are thought to have been derived from the entodermal outgrowth from the cloaca. These include the papillomas of the renal pelvis, transitional celled carcinoma, epidermoid carcinoma, and squamous cell carcinoma.

3. Sarcoma (fig. 4), all those arising from embryonal tissues such as mesonephros, embryonal carcinoma, both juvenile and adult forms. and the mixed embryonal tumors including Wilms.

The only subdivision of this group was the attempt made to evaluate the rapidity of growth by determining if the cells were (a) differentiated or (b) undifferentiated or anaplastic. This subdivision seemed to have been of some significance since in the well differentiated group seventeen survived a 5-year period and of these eleven have survived 10 years. Out of the sixteen undifferentiated group, only one survived the 5-year period and that same patient is still living beyond 10 years. She also had deep therapy following the operation. Of the cases in this group which survived beyond the 5-year period, eleven received x-ray therapy in addition to their surgery and nine did not. See table 3.

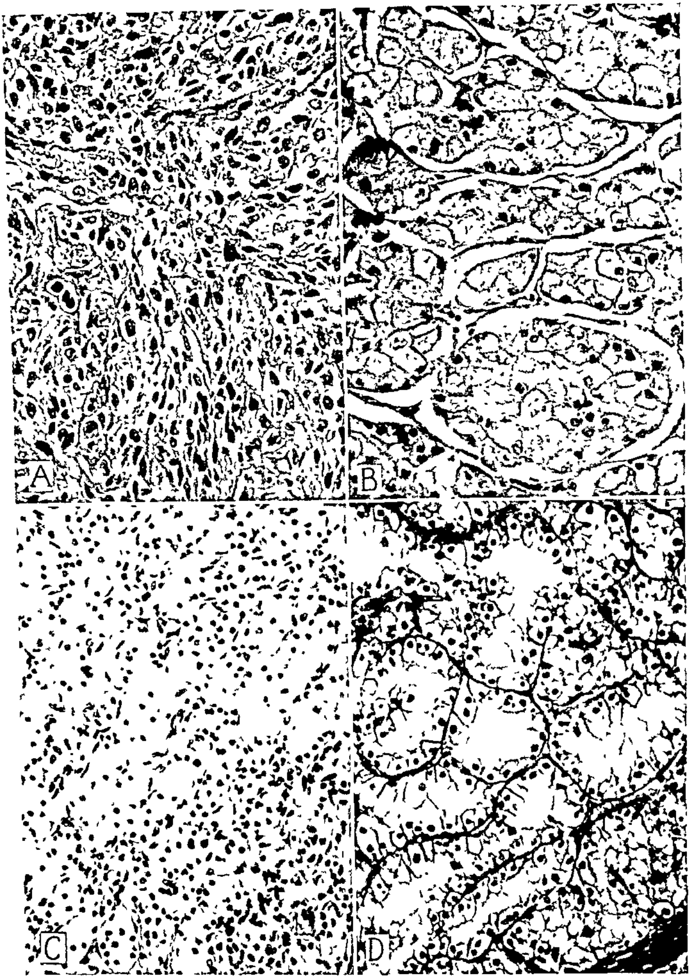

Fig. 2. *A*, anaplastic type of renal adenocarcinoma. Cell margins are poorly differentiated. Cellular cytoplasm varies greatly in amount and nuclear staining is irregular with varying sizes in cellular cytoplasm as well as marked differences in size and staining qualities of nuclei. *B*, well differentiated adenocarcinoma which illustrates highly granular type of distinctly outlined cells [illegible]. Cells are uniform in size and in outline; nuclei of uniform [illegible], small celled type of well differ- [illegible] in outlines of cells and almost no [illegible] ase in group that showed such small cells. *D*, well [illegible] with lacey effect characteristically associated with [illegible] v marked degree of regularity with varying amounts [illegible] ch are approximately same size and regularly placed within cytoplasm. This particular patient is living 16 years after nephrectomy.

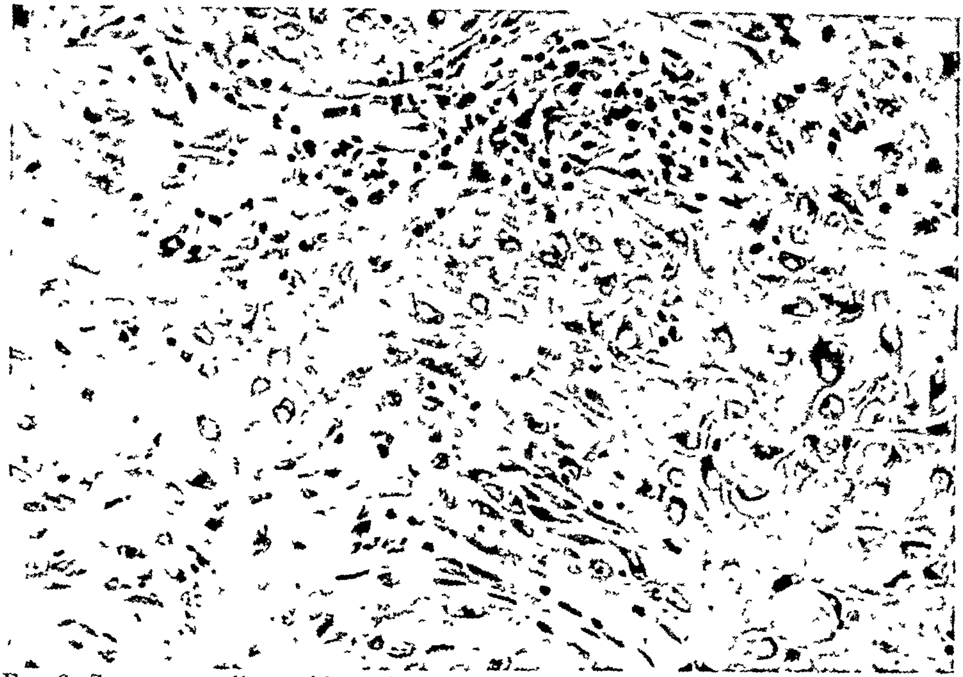

FIG. 3. Squamous cell or epidermoid type of transitional cell carcinoma originating from renal pelvis

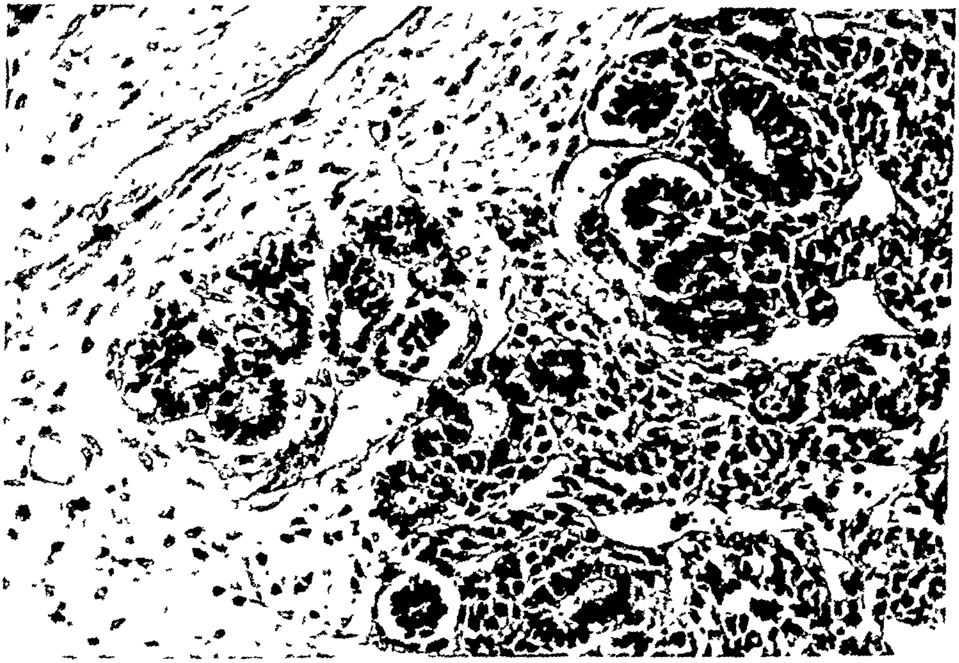

FIG 4. Sarcoma or Wilms's tumor with characteristic rosettes as well as hyperchromatic rapidly growing and undifferentiated cellular structure with very little cytoplasm and irregularly sized nuclei. Adjacent to this is totally different section of tissue with very few nuclei and almost benign appearance in tumor.

The ratio of male to female in this series is still two to one, with the right and left sides being about equally involved. One patient had bilateral papillary cystic adenocarcinoma of the kidneys. These tumor masses were removed 2 months apart in 1947. He is still well apparently without evident metastasis.

TABLE 3. *Survival periods of various tumors*

	5 YEARS	10 YEARS +
Adenocarcinoma		
Well differentiated	17	11
Undifferentiated	1	1
Transitional cell (papillary of pelvis)	1	1
Sarcoma (Wilms)	1	0
Rhabdomyo.	0	0
Leiomyo	1	1
Teratoma	1	0
Totals	22	14

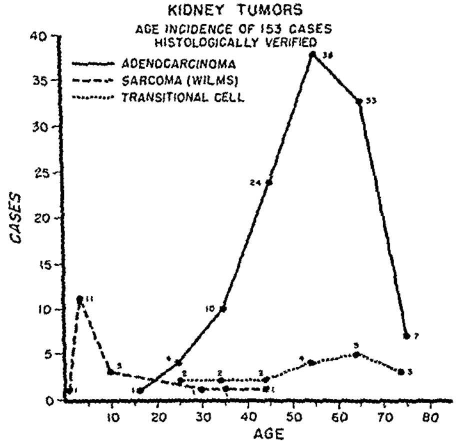

FIG. 5 Analysis of age incidence of three primary groups of kidney tumors. Numerals indicate total cases of particular type of tumor which occurred in each decade

Sarcomas are still most frequently seen in the first three years of life (fig. 5). One case in this group was unusual inasmuch as it was the cause of death of a 6½ month fetus. This kidney with the tumor mass measured 8 by 4 by 6 cm., and weighed 1850 gm. There is also the occasional sarcoma which occurs in the middle years of life. But none was seen after the age of forty-four.

The adenocarcinomas and the transitional cell carcinomas occur over approximately the same age span with the peak of incidence of the former being in the sixth decade and the peak of the latter being in the seventh decade (fig. 5). The ratio, however, was one transitional cell to 6.6 adenocarcinomas. Only one transitional cell tumor survived a 5-year period whereas seventeen adenocarcinomas survived this period following operation.

The means of diagnosing kidney tumors has undoubtedly improved to a great extent in the past few years:

1. By the greater use of retrograde and excretory urography and by our increased experience in interpreting the pyelograms.

2. By the use of perirenal insufflation with oxygen, especially as this procedure has been facilitated with the advent of the presacral injection rather than unilateral perirenal injection of oxygen.

3. By aortography or renal arteriograms whether by way of the translumbar approach or the percutaneous femoral technique.

The operative procedure has been improved with the choice of transperitoneal, thoraco-abdominal and the Nagamatsu techniques. Any one of these is preferred to the usual oblique flank incision especially if the tumor appears to involve the upper pole of the kidney. In any event, should a lumbar approach be used, it would certainly be better to resect the twelfth rib and continue through the rib bed in order to obtain adequate exposure. We are firmly convinced that inadequate exposure not only makes the procedure more difficult for the surgeon but makes it more of a hazard for the patient 1) from the standpoint of blood loss, 2) from the likelihood of tumor cell dissemination, particularly in the presence of renal vein involvement, and 3) inadequate removal of the perirenal fat, fascia and lymph nodes.

The high mortality in the treatment of kidney tumors during the first 20 years of this century was due greatly to the lack of surgical experience in handling them, to the poor anesthesia, and to the great loss of blood during these operations. These factors had been greatly improved at the beginning of this series. But transfusions at the time were not greatly used and blood banks had not been established. Neither had endotracheal anesthesia been used to any extent nor had antibiotics. Consequently, no attempt was made to excise some of the very large tumors 1) because of the fear of exsanguination, 2) because the anesthetic control was not adequate, 3) because the flank incision was used more often than the transperitoneal and in some instances neither of these was adequate.

Now with the aid of blood banks, endotracheal anesthesia by a trained anesthesiologist, the newer approaches via the thoraco-abdominal or the Nagamatsu exposure, much larger tumors can be excised with far greater safety to the patient. Whether the use of these improvements in this new era of well trained urologists will result in a lower mortality rate or a longer period of survival may require another twenty years to determine.

DISCUSSION

In this series of 199 cases of kidney tumors, 102 were nephrectomized; twenty of these survived a 5-year period which is 19.6 per cent of those operated upon or 10 per cent of the total number. Out of the 5-year survivals, thirteen continued to be well for 10 years or more, which represents 12.7 per cent of those subjected to nephrectomy but only 6.5 per cent of the total 199 cases.

Nephrectomy with x-ray therapy seemed to offer a slightly better prognosis than nephrectomy alone but the number of cases in this series is not large enough from which to draw any conclusions. The study of the adenocarcinomas of the renal parenchyma seemed to indicate that the different cellular configurations were merely variants of the same tumor. There were, however, evidences difference in the rate of the growth of the cells in these various tumors. The which had the greatest degree of cellular differentiation and cellular grouping were the slower growing tumors, the cells which were undifferentiated and anaplastic were the more rapidly growing and the more malignant Broders made the same observation 30 years ago In the group of transitional celled tumors of the pelvis there were three of the squamous type, all of which had extensive metastases and caused death within a 1-year period

The greatest weakness in our treatment of these conditions is the lateness of our diagnosis Until the disease can be diagnosed in its early stages, before metastases have occurred, improved surgical treatment will result in very little change in the end results One possible exception here might be the isolation of a radioactive substance to which all or some of the tumors would be sensitive

A better and more hopeful attack would be the routine study of all patients, especially those above the age of 40 years This could be done by performing excretory urography on every patient admitted to our hospitals and those given yearly physical examinations The cost would be no greater than our routine chest x rays The finding of early kidney tumors or other pathological processes in their early stages would warrant the expense

CONCLUSION

Improved diagnostic procedures should enable us to make an earlier and more accurate diagnosis in almost all cases

The improved surgical approaches offer a better exposure for the complete removal of the kidney and perirenal fat with a lessened chance of disseminating tumor cells

Improved anesthesia, an available blood bank and the use of antibiotics lessen the chance of shock and infection

Sarcomas should still be excised and the operation followed by deep x ray therapy In instances which prohibit immediate surgery, deep x ray should precede operation and then follow it

Adenocarcinomas of the renal parenchyma with an anaplastic undifferentiated structure are not likely to survive 5 years

Well differentiated adenocarcinomas without evidence of metastases, which are removed surgically, have one chance in five of surviving 5 years and one chance in eleven of surviving 10 years after the removal of the tumor

Medical Arts Bldg , Pittsburgh 13, Pa (W A B)
Mercy Hospital, Pittsburgh 19, Pa (E J McC)

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URETERAL OCCLUSION BY BARIUM GRANULOMA

JAMES S. ELLIOT AND MILTON L. ROSENBERG*

From the Department of Surgery, Division of Urology, Stanford University School of Medicine, San Francisco, Calif.

Accidental perforation of a viscus during radiographic investigation by barium meal or enema is fortunately an uncommon occurrence. The sequelae to the introduction of barium sulfate into the retroperitoneal tissues by these means are not generally known. Intraperitoneal granulomatous masses due to barium sulfate given by mouth have been described by Fernandez-Crespo.[1] Masshoff[2] and Isaacs[3] have each discussed the formation of granulomatous masses in the peritoneal cavity following perforation of the bowel during barium enema. According to these authors, the introduction of barium sulfate into the tissues is followed by an inflammatory reaction resulting in the formation of a foreign body granuloma. There are no previous reports in the literature concerning the urological complications which may be observed following the introduction of barium sulfate into the retrovesical and retroperitoneal tissue of the pelvis.

A case of this type, in which bilateral ureteral occlusion developed, has recently been observed.

CASE REPORT

A 68-year old woman underwent a barium enema as a routine diagnostic procedure prior to the treatment of a rectal polyp. Films taken after the barium enema disclosed a large retroperitoneal extravasation of barium. On the following day, sigmoid colostomy and drainage of the prerectal space were done in order to reduce the likelihood of severe retroperitoneopelvic infection. The pelvic peritoneum was found to be distended with barium and the rectum was slightly edematous. Antibiotics, consisting of penicillin, streptomycin, and terramycin, were administered during the ensuing 3 weeks. The patient ran a mild febrile course during this period and drained serous fluid, but no barium through the prerectal incision. In other respects, her convalescence was uneventful until approximately 6 weeks after the rectal perforation. At this time, oliguria was noted. Within one week, the oliguria progressed to complete anuria. Nausea and vomiting then developed and the patient became comatose. Blood chemistry studies revealed the blood urea nitrogen to be 131 mg. per cent; the creatinine, 15.6 mg. per cent; carbon dioxide combining power, 17 mm./L; chlorides, 89.7 meq/L; and potassium, 5.4 meq/L. Upon catheterization, the bladder was found to be empty. Catheters were passed up each ureter after

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* Bank of America-Giannini Foundation Research Fellow.

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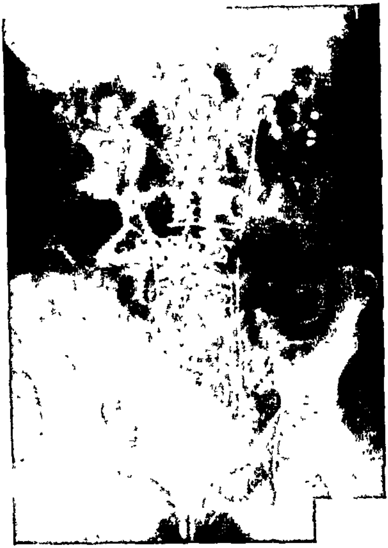

FIG. 1

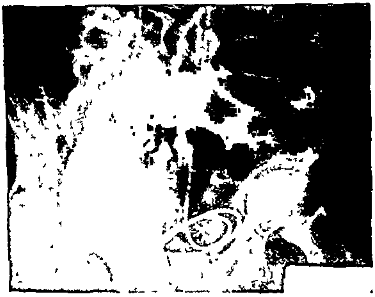

FIG. 2

meeting resistance between 2 cm. and 5 cm. A 6F catheter was left indwelling in each pelvis. Diffuse diuresis ensued with 1000 cc urine being excreted in the following thirty minutes. Within a 24-hour period, the patient excreted 4500 cc urine through the ureteral catheters, and within 48 hours, her blood chemistry had returned to normal. Figures 1 and 2 are views showing ureteral catheters in place and the extravasated barium in the pelvis.

Exploration of the retroperitoneal and retrovesical area was performed one week after cystoscopy. The retrovesical and peri-ureteral areas were found to be involved in a dense, fibrotic mass of inflammatory tissue. Tiny streaks of barium could be observed in the lymphatics. No pools or locules of barium sulfate were encountered. The material appeared to be spread diffusely throughout the pelvis, and the ureters were incorporated in a dense, inelastic mass. Dissection of this mass was exceedingly difficult, and isolation of the ureters was not feasible. It was clearly evident that no definitive surgical treatment was possible. Simple closure was done and convalescence was uneventful.

The ureteral obstruction was treated by continuous indwelling ureteral catheters and ureteral dilatations. The introduction of a larger catheter was performed at, approximately, weekly intervals. Six weeks after the onset of anuria, the patient was discharged from the hospital. At this time, her urinary output was excellent, and 10F catheters could be passed up each ureter to the renal pelvis with ease. Periodic ureteral dilatations were performed over the ensuing 6 months, but there has been no evidence of recurrent ureteral stenosis or occlusion. Excretory urograms were normal 6 months, and, again, 10 months after the initial accident. No change had occurred in the distribution or amount of barium after ten months.

DISCUSSION

In addition to an initial low grade pelvic cellulitis following perforation of the rectum, a foreign body granuloma subsequently developed due to the presence of barium sulfate in the retrovesical tissues, which resulted in complete ureteral occlusion. Exploration of the retrovesical area was attempted with the aim of affording definitive treatment and the hope of actual surgical relief of the extraureteral obstruction. Due to the diffuse, dense, and inelastic nature of the foreign body granulomatous reaction, this proved to be impossible. Conservative management by means of ureteral dilatations has provided complete and, apparently, lasting relief from the obstruction.

CONCLUSION

The introduction of barium sulfate to the retroperitoneal tissues of the pelvis results in the formation of a dense foreign body granulomatous type of inflammation. Involvement of the retrovesical area may lead at a late date to complete ureteral occlusion. Surgical removal of the barium sulfate or relief of the obstruction by surgical means is impossible. The ureteral obstruction has been successfully treated in one case by means of ureteral dilatations and indwelling ureteral catheters.

411—30th St., Oakland 9, Calif. (J. S. E.)

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A NEW CONCEPT OF URINARY BLADDER MUSCULATURE

DeWITT T HUNTER, JR

From the Department of Anatomy, University of Maryland School of Medicine, Baltimore, Md

This paper is directed toward the clarification of the anatomy of the urinary bladder A new concept of bladder musculature is advanced which lays emphasis on the fiber bundle as the structural element rather than the muscular layer

BACKGROUND

The present concept of bladder musculature propounds little more than that the bladder consists of an outer longitudinal, middle circular, and inner longitudinal muscle layer Versari[1] in 1897 and Kalischer[2] in 1900 published works which are largely responsible for this present concept Versari admitted that there was a great deal of muscular anastomosis between the various layers and in addition suggested that the inner longitudinal layer be called the reticular layer because it was more reticular or netlike than longitudinal These anastomoses observed by Versari, balefully disregarded by contemporary anatomists and clinicians, are the crux of the bladder anatomy

METHODS

This investigation was carried out by dissecting twelve bladders to various stages of completion and by illustrating the results in a serial manner Ten of the bladders were male bladders and two were female All of the specimens were removed by wide excision from the cadaver Eleven of the bladders were preserved in standard embalming fluid and were in the contracted state The twelfth bladder was examined in the fresh condition The dissections involved mobilizations of entire muscle layers, the tracing of individual muscle bundles, and combinations of these two techniques The description of bladder musculature which follows can best be confirmed by sectioning a bladder through a plane parallel to and one centimeter from the midsagittal plane and tracing a typical outer longitudinal muscle bundle from its origin to its termination on the inner surface of the bladder (fig 13) All of the dissections and observations were done grossly The trigone, internal sphincter, and ureters have been discussed and illustrated in Uhlenhuth, Hunter and Loechel[3], here they will be referred to only insofar as they are related to the vesical musculature

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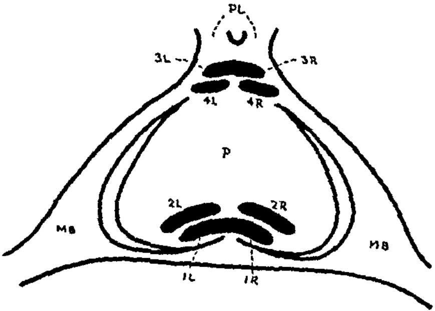

Figure 1

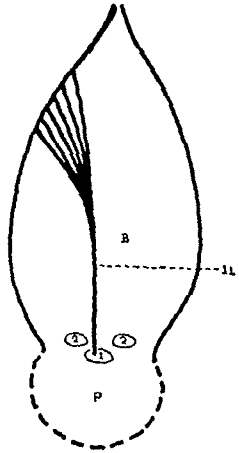

Figure 2

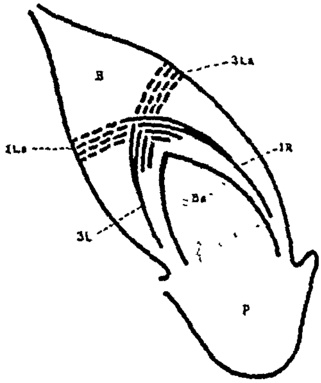

Figure 3

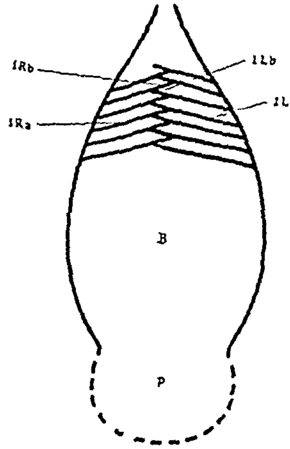

Figure 4

Fig. 1. Dorsocranial view of base of prostate gland. Showing origin of dorsal and ventra layers of outer longitudinal bladder musculature. *1 R*, *1 L*, Right and left halves of dorsa superficial group. *2 R*, *2 L*, Right and left dorsal deep groups. *3 R*, *3 L*, Right and left halves of ventral superficial group. *4 R*, *4 L*, Right and left ventral deep groups. *MB*, musculotendinous band circumnavigating base of prostate. *P*, base of prostate seen from above. *PL*, puboprostatic ligament.

Fig. 2. Dorsal surface of bladder. Showing course of bundle of left half of superficial group of dorsal [illegible] muscle layer. *1 L*, Bundle of left half of superficial group of dorsal outer [illegible]le layer. *B*, dorsal bladder surface. *P*, prostate. *1*, Origin of superficial group. *2*, Origin of deep group.

Fig. 3. Left lateral side of bladder. Showing decussation of bundles of left half of dorsal superficial (*1 R*) with bundles of left half of ventral superficial (*3 L*) group (first decussation). *1 R*, Bundle of left half of superficial group of dorsal outer longitudinal bladder musculature, before decussation. *1 La*, Same bundle having become circular, after first decussation. *3 L*, Bundle of left half of superficial group of ventral outer longitudinal bladder musculature, before decussation. *B*, left lateral side of bladder. *P*, prostate gland. *Ba*, Area on lateral aspect of bladder frequently devoid of longitudinal musculature.

Fig. 4. Ventral bladder surface. Diagram showing decussation of bundles of left half of dorsal superficial group (*1 La*) with bundles of right half of dorsal superficial (*1 Ra*) group (second decussation). *1 La*, Bundles of left half of superficial group of dorsal outer longitudinal bladder musculature, before second decussation. *1 Lb*, Same bundles, after second decussation. *1 Ra*, Bundles of right half of superficial group of dorsal outer longitudinal bladder musculature, before second decussation. *1 Rb*, Same bundles after second decussation. *B*, ventral bladder surface. *P*, prostate gland.

DESCRIPTION

The outer longitudinal musculature of the bladder is arranged in two layers, a dorsal layer (*1 L and R* and *2 L and R* in figure 1 and figure 12 *As*) and a ventral layer (*3 L and R* and *4 L and R* in figures 1 and 12 *Av* and *Bv*) Both layers are stratified into a superficial group (*1 L and R* and *3 L and R* in figures 1 and 12) and a deep group (*2 L and R* and *4 L and R* in figures 1 and 12) The ventral layer is approximately one half the cross section area of the dorsal group

The bundles of the dorsal layer arise from the dorsal portion of the internal sphincter (*1 L and R* and *2 L and R* in figure 1, *7* in figure 10) Some of its fiber bundles penetrate into the middle lobe (fig 11) of the prostate gland in the male The ventral layer arises from the pubic bone by way of the pubovesical ligaments, from the ventrum of the internal sphincter (*6* in figure 10) and from a musculo tendinous band which is attached to the periphery of the base of the prostate gland in the male (*MB* fig 1)

In both the dorsal and the ventral layers the muscle bundles exhibit a fan-shaped arrangement In the superficial groups the fibers of each side sweep forward and, bending to the same side on which they arise, fan out over the lateral aspect of the bladder (*1 L* in figure 2, *1 L* and *1 LL* in figure 8, *1 L* and *1 LL* in figure 12 *As*, *3 L* and *3 LL* in figure 12 *Av*), while in the deep group the muscle bundles fan out to the side opposite that of their origin (*2 R* and *2 L* in figure 5, *2 R*, *2 RR* and *2 RRR* in figure 8, *2 L* in figure 12 *Bs*, *4 L*, *4 LL* and *4 LLL* in figure 12 *Bv*)

Dorsal and ventral superficial groups of outer longitudinal bladder musculature I shall describe first the behavior of the bundles of the superficial groups A muscle bundle of the superficial group on the left side of the dorsal bladder surface* will serve as an example (*1 L* in figure 2)

A typical muscle bundle of this group on the left side of the bladder sweeps forward over the dorsal surface and curves to the lateral aspect of the same side of the bladder, where it breaks up into smaller muscle bundles These decussate with similar bundles of the superficial group (*3 L* in figure 3) of the left side of ventral bladder surface (see also *1 L* and *1 La* in figure 9) This decussation is the first decussation of the bundles of the superficial groups It takes place in such a manner that the bundles come to lie in a deeper stratum after the decussation than they were lying before the decussation (*1 L* and *1 La* in figure 9) Having decussated the small bundles reunite and again form thicker bundles, which turning at right angles to the original direction (*1 La* in figure 3) become circular in direction and run to the ventral bladder surface (*1 La* in figure 9)

It becomes evident then that the longitudinal bundles of the superficial groups give rise to a deep circular stratum by the simple process of decussating with corresponding bundles of the superficial group of the opposite bladder surface, but of the same side, and by turning into a circular direction after decussation

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* The conventional distinction of a dorsal and a superior bladder surface though justified, holds good only in well contracted bladders For the purpose of describing bladder musculature I shall use mostly the term "dorsum" for both dorsal and superior bladder surfaces

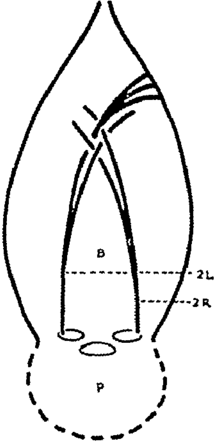

Figure 5

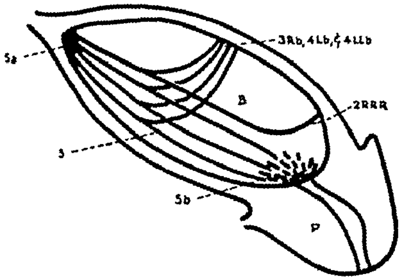

Figure 6

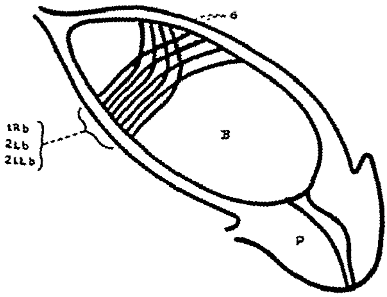

Figure 7

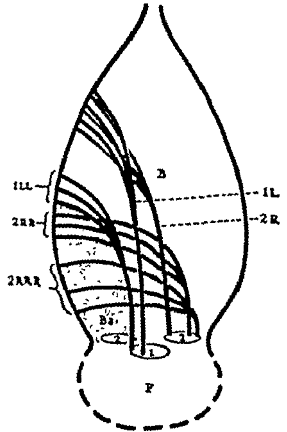

Figure 8

FIG. 5. Dorsal bladder surface. Showing first decussation (on same surface on which they take origin) of most superficial bundles of left and right deep groups of dorsal longitudinal bladder musculature (first decussation). Note that bundles of deep groups undergo decussation (first decussation) while they are still on bladder surface on which they take origin. Since they partake in both decussations of superficial groups, they decussate three times. *2 L*, Most superficial bundle of left deep group of dorsal outer longitudinal bladder musculature. *2 R*, Corresponding bundle of right deep group. *B*, Dorsal bladder surface. *P*, prostate gland.

FIG. 6. Left lateral bladder surface. Inner longitudinal bundles (*5*) on ventral bladder surface derived from bundles of ventral outer longitudinal groups (*3* and *4*) after their last decussation. *2 RRR*, anastomosis of some of deepest (basal) bundles of right deep group of dorsal outer longitudinal bladder musculature with *3 Rb*, *4 Lb* and *4 LLb*, bundles of right superficial and left deep groups of ventral outer longitudinal bladder musculature coming down on left side of bladder after their second and third decussations, respectively (see figure 9) and forming *5*, ventral inner longitudinal bundles. *5 a*, Star-shaped mass of vortex of bladder. *5 b*, Muscle plate (over inner surface of internal orifice of urethra. *B*, left lateral bladder surface. *P*, prostate.

FIG. 7. Left lateral bladder surface. Circular bundles from right superficial and left deep groups (see fig. 9) of dorsal outer longitudinal bladder musculature, after their last decussation, break up into inner reticular bundles on inner dorsal bladder surface. *1 Rb*, Bundles from right half of superficial group of dorsal outer longitudinal bladder musculature, after their last (second) decussation. *2 Lb* and *2 LLb*, bundles from left deep group of dorsal outer longitudinal bladder musculature, after their last (third) decussation *6*, Reticular bundles on inner dorsal bladder surface. *B*, left lateral bladder surface. *P*, prostate gland.

FIG. 8. Dorsal bladder surface. Showing course of muscle bundles of superficial and deep groups of dorsal outer longitudinal layer of bladder musculature. *1*, Superficial group of dorsal outer longitudinal layer of bladder musculature. *2*, *2*, Deep groups of dorsal outer longitudinal layer of bladder musculature. *1 L*, *1 LL*, Bundles of left half of superficial group. *2 R*, Most superficial bundle of right deep group. *2 RR*, Deeper bundles of right deep group. *2 RRR*, Deepest bundle of right deep group (transverse bundle of bladder base). *B*, dorsal surface of bladder. *Ba*, Shaded area represents region usually devoid of longitudinal bundles. *P*, prostate gland.

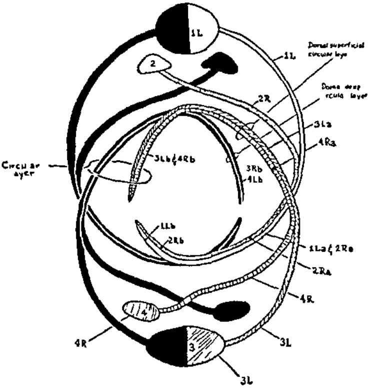

FIG 9 Showing course and decussation of bundles of six different groups of outer longitudinal bladder musculature, projected upon transverse plane Diagram may be used to figure out derivation of bundles in circular layer in different regions of bladder wall as well as location of five different decussations *1 L* Origin of dorsal superficial group of left outer longitudinal bladder musculature *2*, Origin of dorsal deep groups of outer longitudinal bladder musculature *3 L*, Origin of ventral superficial group of outer left longitudinal bladder musculature *4*, Origin of ventral deep groups of outer longitudinal bladder musculature *1 L* and *3 L*, Bundles of left half of superficial group of dorsal (ventral) longitudinal layer before first decussation *1 La* and *3 La* Same bundles after first decussation *1 Lb* and *3 Lb*, Same bundles after second decussation *2 R* and *4 R*, Bundles of right deep groups of dorsal (ventral) outer longitudinal layer after first decussation

As we have seen, this behavior is true for the superficial groups of both the dorsal and ventral bladder musculature

We will continue to follow the bundle *1 L* in figure 2, with which we started When this and similar bundles, now circular (*1 La* in figures 3, 4 and 9) arrive in the ventral midline of the bladder, they decussate again (second decussation), this time, however, with the bundles from the superficial group of the same bladder surface, but of the opposite side (*1 Ra* in figures 4 and 9) Again the decussation is of that kind that these bundles are carried into a still deeper circular stratum of the muscular wall of the bladder (*1 Lb* in figures 4 and 9) And again exactly the same behavior is found for the bundles of the superficial groups of both the dorsal and ventral longitudinal layers with the one exception that the second decussation of the dorsal bundles takes place on the ventrum of the bladder, while that of the ventral bundles occurs on the dorsum of the bladder The second decussation of the ventral superficial group is shown in an actual dissection at *3* and *4* of figure 12 *Cs*

We have followed now the bundles of the superficial groups of the outer longitudinal muscle layers into the deepest circular layer and shall leave them at that point of their course Their final fate will be taken up when the continuations of all circular bundles will be described

We shall now turn to a description of the deep groups (*2 L and R* and *4 L and R* in figure 1) of the outer longitudinal muscle layers

Deep groups of outer longitudinal bladder musculature The muscle bundles of

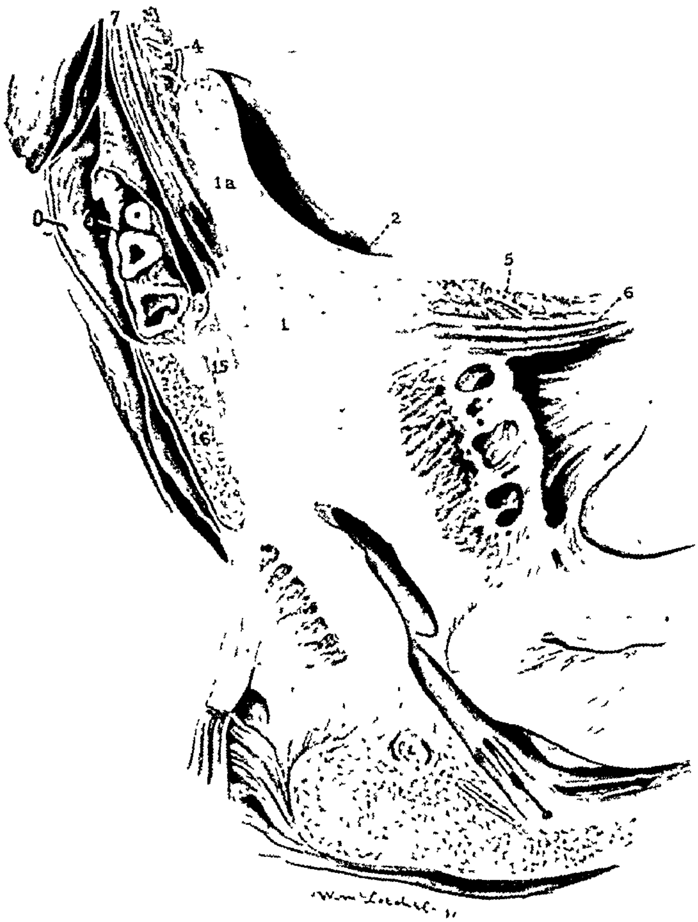

FIG. 10. Sagittal section through base of bladder, somewhat to right of midsagittal plane. Natural size (from Uhlenhuth, Hunter, Loechel · *Problems in the Anatomy of the Pelvis*, 1952, fig. L_2). Showing origin of outer longitudinal bladder musculature from internal sphincter. *1*, Internal sphincter. *1 a*, Trigonal portion of internal sphincter. *2*, Internal orifice of urethra. *4*, *5*, Circular bladder musculature *6*, Ventral outer longitudinal layer of bladder musculature. 7, Dorsal outer longitudinal layer of bladder musculature. *15*, Middle lobe of prostate. *16*, Dorsal lobe of prostate.

the deep groups of outer longitudinal musculature become likewise circular, but differ in some details of their course from the superficial groups.

The deep groups arise deep to and under the lateral margins of the superficial groups (*2 L and R* and *4 L and R* in figure 1; *2 L* in figure 12 *Bs*; *4 L*, *4 LL* and *4 LLL* in figure 12 *Bv*; see also *11 a* in figure M_3 of Uhlenhuth, Hunter, Loechel: *Problems in the Anatomy of the Pelvis*, 1952).

With the exception of the deepest bundles (transverse bundles of the bladder base) of the deep groups (*2 RRR* in figure 8), which become circular almost immediately after their origin, the bundles of the deep groups, like those of the superficial groups, pass forward over the dorsal and ventral bladder surfaces. But unlike the bundles of the superficial groups they curve in a medial direction so that ultimately they arrive at the lateral aspect of the bladder on the side opposite to the side of their origin (*2 L* and *2 R* in figure 5; *2 R* and *2 RR* in

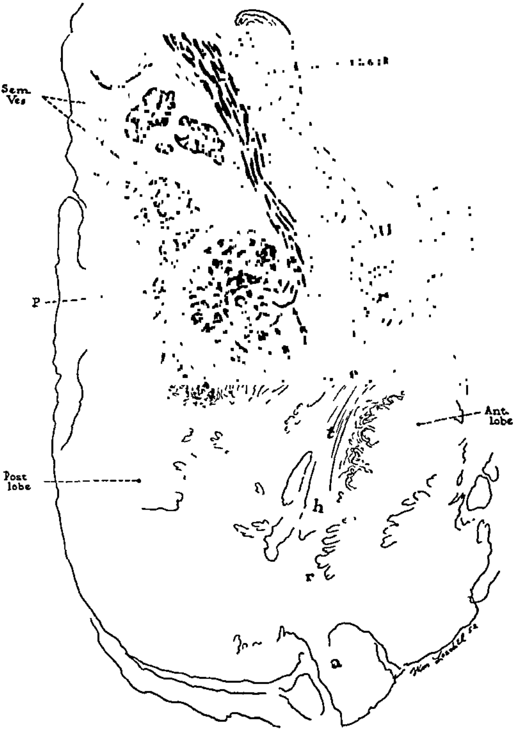

FIG 11. Sagittal section through bladder base and prostate gland, showing dorsal outer longitudinal bundles of bladder wall, which penetrate into middle lobe of prostate gland. *1 L* and *1 R*, Dorsal outer longitudinal musculature. *1*, Bladder fibers penetrating middle lobe of prostate. *P*, Middle lobe of prostate. *T*, Trigone.

figure 8; *2 L* and *2 LL* in figure 12 *Bs*). Moreover, before they reach the lateral margins of the bladder, they decussate with the bundles of the deep group of the same bladder surface but of the opposite side (*2 L* and *2 R* in figure 5; *2 L* in figure 12 *Bs*). This is the *first decussation* of the deep groups.

After this decussation, as they approach the lateral aspect of the bladder they break up into thinner bundles, become circular and intermingle with the circular bundles from the superficial groups (*1 L* and *2 R* in figure 8). Following the same course as these, they cannot any longer be distinguished from them. Since they participate in the two decussations of the bundles of the superficial groups, it is obvious that the bundles of the deep groups undergo three decussations.

We are now ready to discuss the final fate of all the circular bundles. Having become organized into circular bundles in the bladder wall opposite that of their

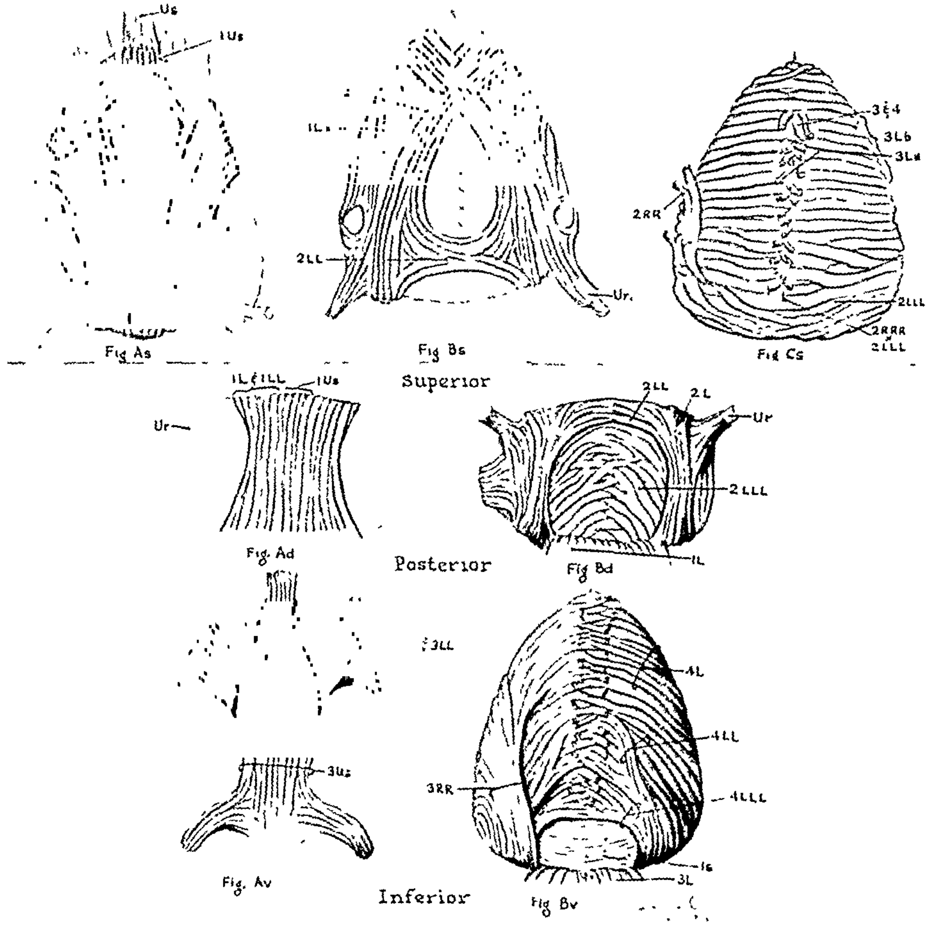

FIG. 12. Dissection of bladder of a white male, 62 years old (dissection 479_{64}), illustrated at different stages in superficial, dorsal, and ventral bladder surfaces. *1 s* to *3 s*, Superior surface; *1 d*, *2 d*, dorsal surface; *1 v*, *2 v*, ventral surface. *As*, Fascial capsule had been removed. *1 Us* are central bundles of dorsal superficial group which run to vortex of bladder, become greatly attenuated and accompany urachus (*Us*). On either side of this central superficial group are located more lateral and deeper groups (*1 L* and *1 LL*) of superficial layer. Deep to these are seen longest and most superficial bundles of deep groups (*2 L*). *Bs*, Superficial group (*1 Us*, *1 L* and *1 LL*, in *As*) and most superficial bundles of deep group (*2 L*) of dorsal outer longitudinal layer have been removed. Medially some more of more superficial bundles of deep groups (*2 L*) are exposed. Centrally and dorsally some of next deeper and shorter bundles (*2 LL*) of deep groups are seen. First decussation of deep bundles is visible. Laterally a group of bundles (*1 Lx*) was located in this bladder, which represent transition between bundles of superficial and deep group. At *Ur* we see ureter covered by outer longitudinal bladder musculature forming part of its outer longitudinal muscle layer. *Cs*, Most of bundles of superficial and deep groups including superficial stratum of circular bundles, have been removed to expose circular fibers (3 and *4*) which come from ventral groups of outer longitudinal muscle layer. They are seen decussating along midline. Most dorsal end of line of decussation is formed, however, by very deepest bundles (*2 RRR* and *2 LLL*) of dorsal deep groups (transverse bundles of bladder base). At *2 RR* some of deeper bundles of right deep group are left; their first decussation is visible. *Ad*, Superficial group as it looks in dorsal view of bladder, after fascial capsule has been removed. *Bd*, Superficial group (*1 L*) has been raised and reflected. At *2 L* and *2 LL* more superficial bundles of deep groups and their decussations are seen, at *2 LLL* very deepest (transverse basal) bundles of deep groups and their decussations are visible. *Av*, Fascial capsule has been removed from ventral bladder surface, to expose ventral outer longitudinal layer, parts of which are indicated at *3 Us* (central bundles of ventral superficial group which accompany urachus) and at *3 L* and *3 LL* (more lateral bundles of superficial group). At *4 L* some of longest bundles of deep groups are exposed. *Bv*, Most of ventral superficial group (*3 L*) has been lifted and reflected; laterally at *3 RR* deeper portion of superficial group can be seen. In median line first decussation of bundles (*4 L*, *4 LL*) of ventral deep groups and, further dorsal, decussations of deepest bundles (transverse basal) of ventral deep groups (*4 LLL*) are visible. At *Is*, dorsal to transverse basal bundles, ventral sector of internal sphincter is exposed.

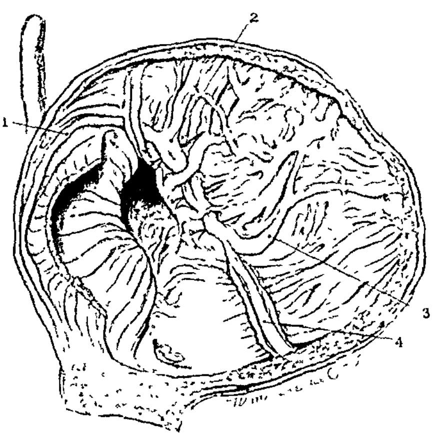

FIG. 13 Bladder dissection showing individual bundle traced from its origin to its many terminations. (This fibe [illegible] off by circular bundle prior to its first decussation.) [illegible] 1 cm. from its midline and mucosa was raised and rer [illegible] 39 years old.) *1*, Dorsal longitudinal bundles of superficial group. *2*, Its continuation into circular bundles. *3*, Continuation of circular bundle into longitudinal bundle of innermost layer. *4*, Continuation of same circular bundle to ventral bladder wall.

origin, the bundles from both the superficial and deep groups dissipate themselves into small bundles which constitute the innermost or third layer of the muscular wall of the bladder.

Final distribution of circular bundles from the ventral layer. The circular bundles from the ventral layer, having traversed the dorsum of the bladder break up into thinner bundles (*3 Rb*, *4 Lb* and *4 LLb* in figures 6 and 9) which pass down to the ventral bladder surface and there align themselves with the bladder axis on the inner surface of the ventral wall (*5* in figure 6; *3* in figure 13). Apically these inner longitudinal bundles converge at the vertex of the bladder and there form a stellate mass (*5 a* in figure 6). Basally these bundles, with the exception of the most lateral, subdivide still further, forming a muscular plate (*5 b* in figure 6) which is situated along the lateral and ventral periphery of the internal orifice of the urethra and gives rise to a thick layer of lateral and ventral inner longitudinal musculature of the urethra (see *17* and *17 a* in figures M_1 and M_2 of Uhlenhuth, Hunter, Loechel: *Problems in the Anatomy of the Pelvis*, 1952).

The more lateral of these inner longitudinal bundles becomes continuous, dorsally, with the transverse basal bundles of the dorsal bladder wall (*2 RRR* in figure 8) to be described presently. One or several of these lateral bundles arches over the superolateral aspect of the ureteral orifice and have been described and illustrated in Uhlenhuth, Hunter and Loechel, 1952 (*22 f'* in figure J_{14}; *5 b* in figure L_1; and *14 R*, *14 L* in figure M_1). Evidently these bundles have the function of a sphincter of the orifice of the ureters.

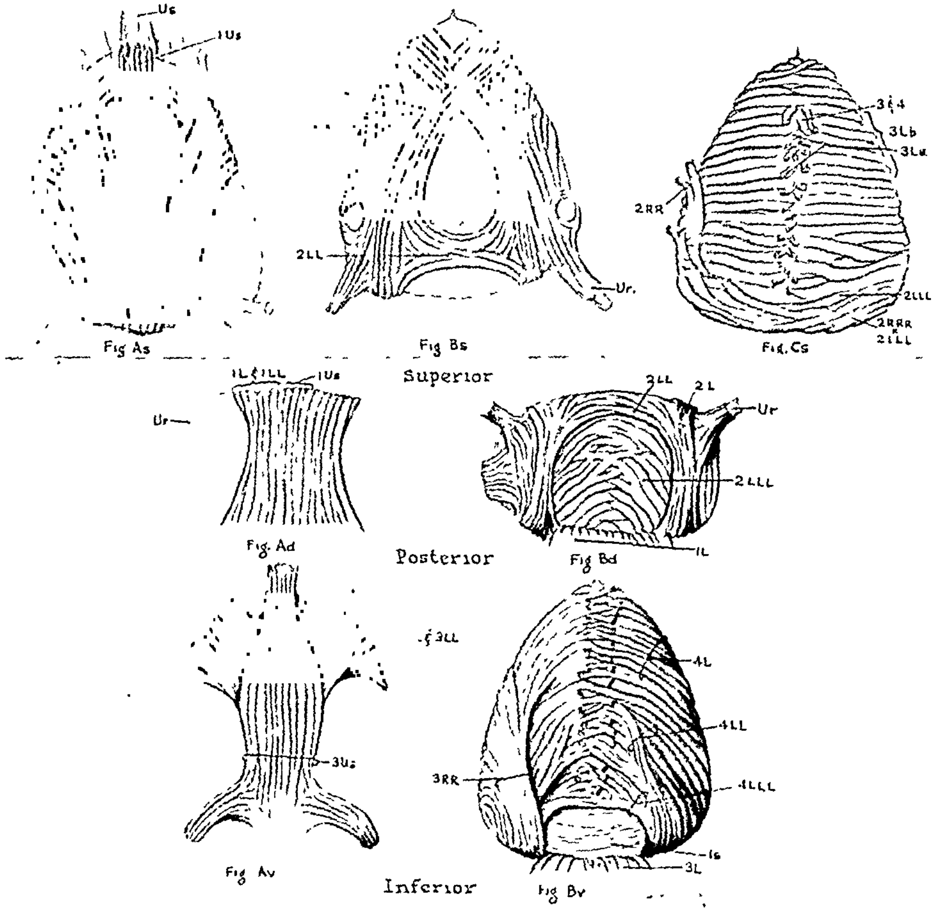

FIG. 12. Dissection of bladder of a white male, 62 years old (dissection 479_{64}), illustrated at different stages in superficial, dorsal, and ventral bladder surfaces. *1 s* to *3 s*, Superior surface; *1 d*, *2 d*, dorsal surface; *1 v*, *2 v*, ventral surface. *As*, Fascial capsule had been removed. *1 Us* are central bundles of dorsal superficial group which run to vortex of bladder, become greatly attenuated and accompany urachus (*Us*). On either side of this central superficial group are located more lateral and deeper groups (*1 L* and *1 LL*) of superficial layer. Deep to these are seen longest and most superficial bundles of deep groups (*2 L*). *Bs*, Superficial group (*1 Us*, *1 L* and *1 LL*, in *As*) and most superficial bundles of deep group (*2 L*) of dorsal outer longitudinal layer have been removed. Medially some more of more superficial bundles of deep groups (*2 L*) are exposed. Centrally and dorsally some of next deeper and shorter bundles (*2 LL*) of deep groups are seen. First decussation of deep bundles is visible. Laterally a group of bundles (*1 Lx*) was located in this bladder, which represent transition between bundles of superficial and deep group. At *Ur* we see ureter covered by outer longitudinal bladder musculature forming part of its outer longitudinal muscle layer. *Cs*, Most of bundles of superficial and deep groups including superficial stratum of circular bundles, have been removed to expose circular fibers (3 and *4*) which come from ventral groups of outer longitudinal muscle layer. They are seen decussating along midline. Most dorsal end of line of decussation is formed, however, by very deepest bundles (*2 RRR* and *2 LLL*) of dorsal deep groups (transverse bundles of bladder base). At *2 RR* some of deeper bundles of right deep group are left; their first decussation is visible. *Ad*, Superficial group as it looks in dorsal view of bladder, after fascial capsule has been removed. *Bd*, Superficial group (*1 L*) has been raised and reflected. At *2 L* and *2 LL* more superficial bundles of deep groups and their decussations are seen, at *2 LLL* very deepest (transverse basal) bundles of deep groups and their decussations are visible. *Av*, Fascial capsule has been removed from ventral bladder surface, to expose ventral outer longitudinal layer, parts of which are indicated at *3 Us* (central bundles of ventral superficial group which accompany urachus) and at *3 L* and *3 LL* (more lateral bundles of superficial group). At *4 L* some of longest bundles of deep groups are exposed. *Bv*, Most of ventral superficial group (*3 L*) has been lifted and reflected; laterally at *3 RR* deeper portion of superficial group can be seen. In median line first decussation of bundles (*4 L*, *4 LL*) of ventral deep groups and, further dorsal, decussations of deepest bundles (transverse basal) of ventral deep groups (*4 LLL*) are visible. At *Is*, dorsal to transverse basal bundles, ventral sector of internal sphincter is exposed.

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POTENTIALITIES OF BLADDER EPITHELIUM

F K MOSTOFI

From the Armed Forces Institute of Pathology, Veterans Administration Central Laboratory for Pathologic Anatomy and Research, Washington, D C

I am honored to be invited to participate in the panel on bladder tumors with such a distinguished group of urologists Instead of a review of the morphology of vesical epithelial tumors, my presentation will consist of a discussion of the potentialities of the transitional epithelium* that normally lines the bladder A knowledge of these potentialities, I believe, is essential for the proper understanding of the pathology of the epithelial tumors of bladder

POTENTIALITIES OF VESICAL EPITHELIUM

The transitional epithelium of bladder is capable of A) nonneoplastic proliferation, B) "metaplasia" into squamous, columnar, and cuboidal cells, C) neoplasia, not only to transitional, but also to squamous and glandular tumors

A *Nonneoplastic proliferation* Of the six or seven lesions of the urinary vesicle grouped under "granular or proliferative lesions" of the bladder[4, 5, 6] attention may be focused on two polypoid cystitis and cystitis glandularis and cystica

Polypoid cystitis is characterized by edema, congestion, and chronic inflammatory cell infiltration in the wall of the bladder, usually confined to the lamina propria Thin or broad polypoid projections of this inflamed edematous wall, sometimes ulcerated, sometimes covered by epithelium, project into the lumen In later stages of the disease as healing takes place, the epithelium proliferates to form small villous projections (fig 1) A similar picture is seen in the bladder mucosa overlying a sarcoma or a secondary tumor Thus, in response to inflammatory reaction or chronic irritation, eventually an outward proliferation of the bladder mucosa takes place—a growth away from the lamina propria—

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* Read at annual meeting, American Urological Association, Atlantic City, N J June 26, 1952

* The term transitional cell was introduced in 1841 by Henle[1] to designate epithelial cells that are intermediate between stratified squamous and simple columnar Although the exact number of layers and types of cells in the vesical mucosa is a matter of controversy among anatomists there is general agreement that in contracted bladder the cells of the superficial layer are cuboidal, have a cuticular border, and a dark, granular cytoplasm ty These cells have one or two large vesicular nuclei and columnar, and either pseudostratified or multi cells of the superficial layer are flat and indistinguishable from squamous cells, those of the deeper layer are low columnar or cuboidal It is believed that to assume this pattern the cells not only flatten, but actually slip past one another[2, 3]

[1] Henle, F G J Allgemeine Anatomie Leipzig, 1841 p 224

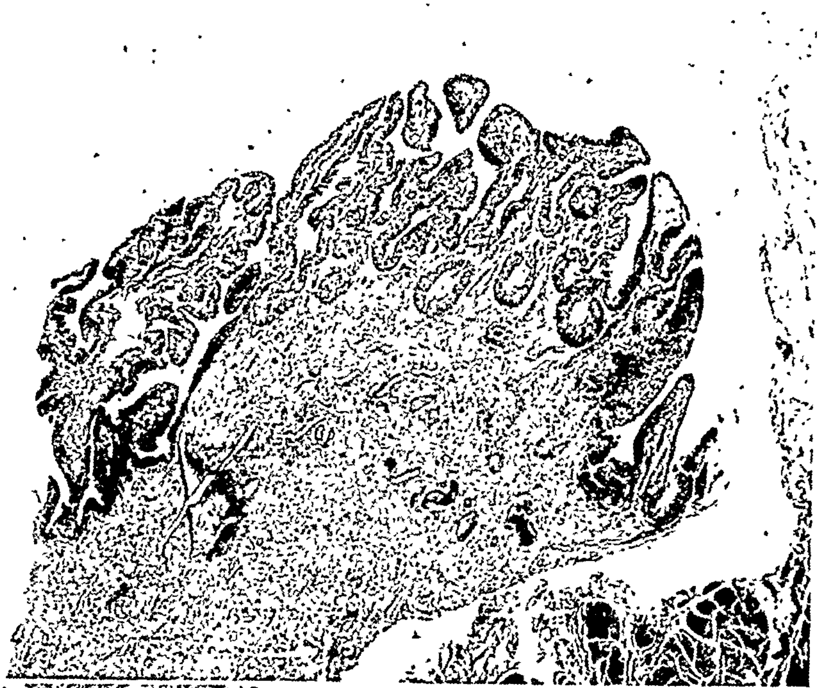
[2] Schaffer, J Das Epithelgewebe, In von Mollendorff, W *Handbuch der mikroskopischen Anatomie des Menschen* Berlin J Springer, 1927, vol 2 pt 1, pp 19–23

[3] Bremer, J L and Weatherford, H L Textbook of Histology, ed 6, Philadelphia Blakiston Company, 1944 p 475

[4] Hinman, F and Cordonnier J Cystitis follicularis J Urol, **34** 302–308, 1935

[5] Stirling W C and Ash J E Chronic proliferative lesions of the urinary tract J Urol, **45**. 312–359 1941

[6] Morse, H D Etiology and pathology of pyelitis cystica, ureteritis cystica, and cystitis cystica Am J Path, **4** 33–49, 1928



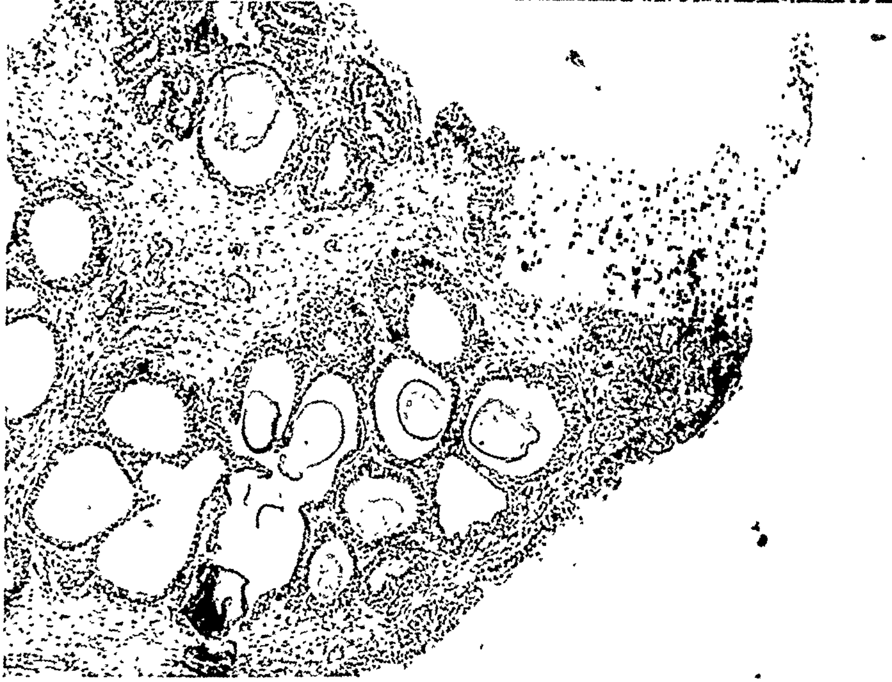


Fig. 1 (upper). Polypoid cystitis. ×21. AFIP Accession 479429
Fig. 2 (lower). Glandular cystitis. ×62. AFIP Accession 109457

which may remain as benign polypoid cystitis for years, or may assume autonomous growth and form papillary tumors.[7-9]

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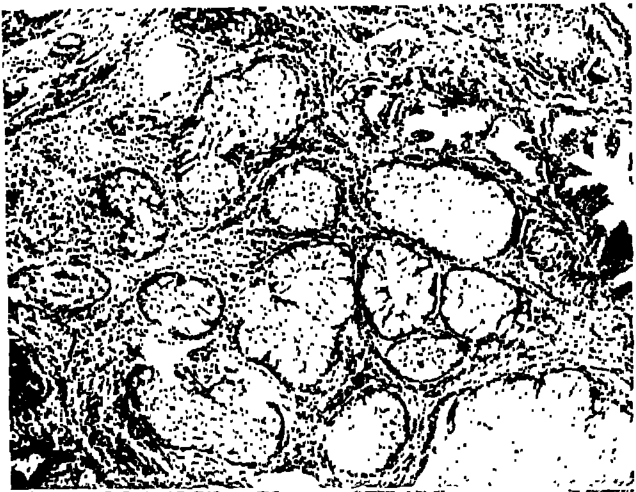
[7] Cahen, F.: Zur Casuistik des Blasentumoren. Virch. Arch. f. path. Anat., **113:** 468–474, 1888.

[8] Stoerk, O.: Beiträge zur Pathologie der Schleimhaut der harnleitenden Wege. Beitr. z. path. Anat. u. z. allg. Path., **26:** 367–445, 1899.

[9] Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia: W. B. Saunders Co., 1942, p. 943.



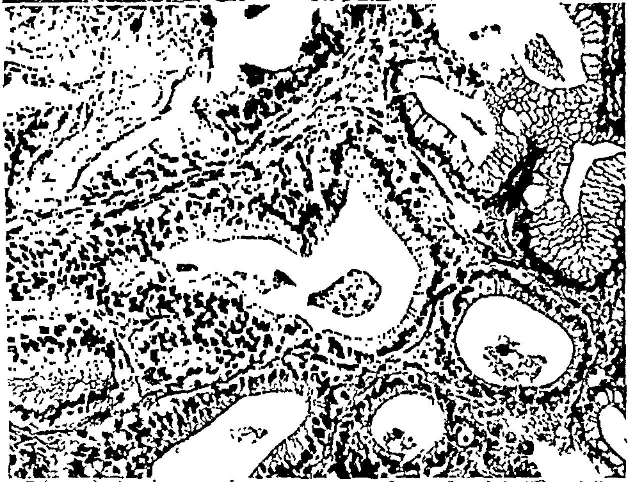


Fig 7 (upper). Another area from same case as figures 5 and 6. "Enteric" mucous glands and, to the right, cystitis glandularis. ×125. AFIP Accession 530992.

Fig 8 (lower). Another area from same case as figures 5, 6 and 7. Cystitis glandularis and mucous glands. A glandular structure at center is partly lined by tall mucus-containing epithelium. ×192. AFIP Accession 530992.

there is a small space lined by transitional epithelium with a superficial layer of cuboidal cells and a deeper layer of club-shaped or columnar cells. One of four things may take place: the epithelial buds may remain as Brunn's nests and glands; they may become increasingly cystic to form cystitis cystica; they may

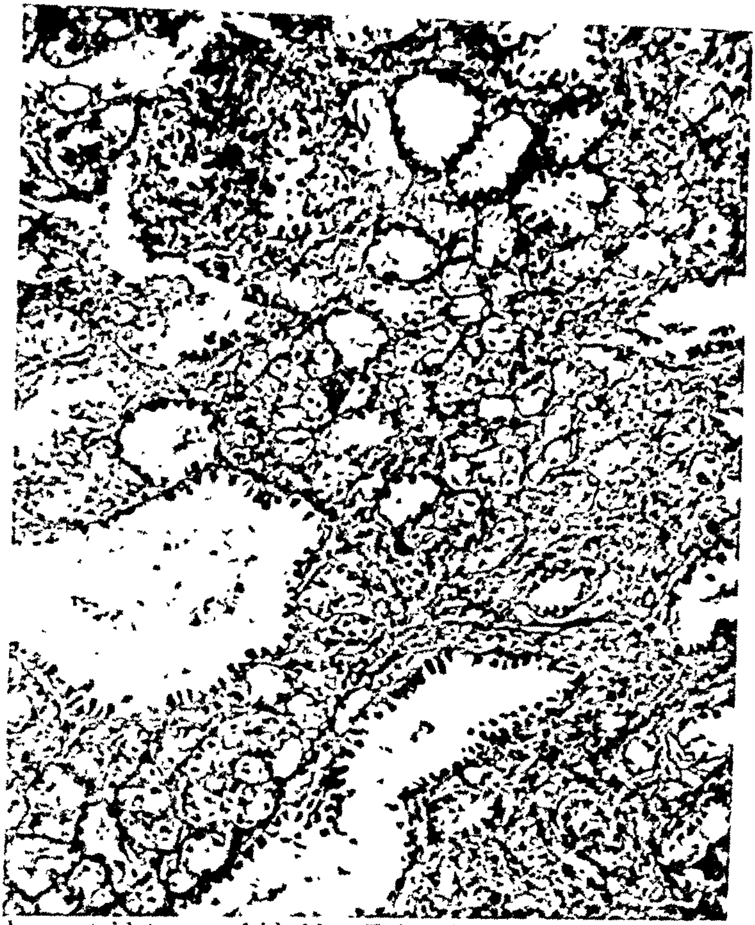


Fig. 9. Adenomatoid tumor of bladder. Epithelial tubules lined by a single layer of epithelium, some showing cystic dilatation. ×100. AFIP Accession 214099.

develop carcinomas; or they may differentiate into true glands. The mechanism of true gland formation[27-30] is believed to be as follows: in some of these epithelial nests a distinct lumen is formed, around which the innermost cells become oriented with their long axes arranged radially toward the central lumen (fig. 6). Mucus appears in the cytoplasm of these cells which assume a columnar shape. In some nests the deeper layers of transitional epithelium lining the glands persist (fig. 7). In others, probably as a result of pressure from the accumulating secretion in the lumen, the deeper cell layers disappear, leaving a glandular structure lined by columnar epithelium. This structure would be indistinguishable from enteric mucosa except that all stages from glandular and cystic cystitis to mucus-containing glands (fig. 8) can be identified. The alteration of transi-

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[27] Brunn, A. von: Ueber drüsenähnliche Bildungen in der Schleimhaut des Nierenbeckens, des Ureters, und der Harnblase beim Menschen. Arch. f. mikr. Anat., 41: 294–303, 1893.

[28] Limbeck, R. von: Zur Kenntniss der Epithelcysten der Harnblase und der Ureteren. Ztsch. f. Heilk., 8: 55–66, 1887.

[29] Lubarsch, O.: Ueber cysten der ableitenden Harnwege. Arch. f. mikr. Anat., 41: 303–323, 1893.

[30] Stoerk, O. and Zuckerkandl, O.: Über cystitis glandularis und den Drusenkrebs der Harnblase. Ztschr. f. Urol., 1: 1–41, 1907.

tional epithelium into mucous epithelium is not confined to glands but also has been demonstrated in the surface epithelial cells[31]

Both Brunn's nests and cystitis glandularis have been observed in the bladders of aniline dye workers and in the spontaneous and experimentally induced bladder tumors of animals[10]

The exact nature of the etiologic agents producing Brunn's nests, cystitis glandularis, cystitis cystica, and true gland formation is unknown, but irritation, infection, and mechanical obstruction of Brunn's nests have been regarded as possibilities Perhaps either metabolic changes in the tissue or urine, or the presence of certain organisms in the urinary tract may bring about histochemical changes in the cytoplasm of epithelial cells, with the formation of mucus Whatever the cause, there is little doubt that mucous epithelium and mucous glands develop through the mechanism that has been presented Autonomous growth of this tissue results in the formation of adenocarcinomas of bladder

3 Cuboidal epithelium Holmes,[32] in a study of a group of gunshot and other wounds of bladder, has observed an unusual lesion At the time of operation, soon after trauma, the vesical mucosa showed no tumors Later on, however, a small tumor appeared which was characterized microscopically by the formation of epithelial tubules lined by a single layer of cuboidal or low columnar epithelium The tubules, some of which showed cystic dilatation, simulated renal collecting tubules (fig 9) The transitional epithelium itself was replaced by low columnar or cuboidal cells forming small papillae There was no mucus Holmes was of the opinion that the lesion was a manifestation of the metaplastic potentiality of vesical epithelium It is of interest that a similar lesion was described by Friedman and Kuhlenbeck[33] as an adenomatoid tumor of the bladder, and interpreted as nephrogenic adenoma "The microscopic picture suggested a renal, either mesonephric or metanephric pattern" to these authors, but they could not exclude "the possibility of postnatal development of such tumors from apparently normal bladder mucosa"[33] Our experience confirms Holmes' observation and leads us to regard the so called nephrogenic adenoma of Friedman and Kuhlenbeck as a manifestation of metaplastic behavior of vesical epithelium The rarity of the lesion and the paucity of tissue from these cases have made it impossible to study the steps in the development of this lesion It may be stated that these patients should be carefully watched as nephrogenic adenoma may develop into carcinoma of the bladder[31]

It is evident from this discussion that although the transitional epithelium of bladder is morphologically different from the squamous, cuboidal, and columnar mucous producing epithelium found in the urinary bladder, they are closely related 1) the transitional epithelium may give rise to these types as has been demonstrated, 2) they may co exist with the transitional epithelium in the same bladder[17, 32] If these premises are correct, and the evidence seems to be in favor of such a concept, then the occurrence of some of the unusual neoplasms of the urinary bladder, i.e., squamous cell carcinoma, adenocarcinoma, nephrogenic adenoma, etc., is an expression of the potentialities of the vesical epithelium, and an indication of a definite increase in the growth activity of the cells.

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[31] Mostofi, F K Unpublished data

[32] Holmes, R H Personal communication

[33] Friedman N B and Kuhlenbeck, H Adenomatoid tumors of the bladder reproducing renal structures (nephrogenic adenomas) J Urol, 64 657-670, 1950

C. *Neoplastic potentiality of the vesical epithelium.* The vesical epithelium is capable of neoplasia into a variety of epithelial tumors, from unmistakable transitional cell tumors with an arrangement of cells that is indistinguishable from that of normal vesical epithelial lining, to other tumors in which there is *not the remotest* suggestion of transitional epithelium. Indeed, some years ago, Dart[31] described 17 cellular variants in epithelial tumors of bladder.

Transitional tumors may arise a) directly from the surface epithelium, b) through polypoid cystitis, c) through the formation of Brunn's nests, or from a combination of all three. Histologically the tumors may be benign or malignant, well differentiated or undifferentiated, papillary or sessile, superficial or infiltrating.

Squamous cell tumors may arise a) directly from the transitional epithelium, b) after squamatization and leukoplakia of the surface epithelium, or c) as a result of alterations in the tumor cells of an erstwhile transitional cell carcinoma. Indeed, in a substantial number of infiltrating transitional cell carcinomas areas of squamous cells and squamous cell carcinoma may be seen.

Adenomas and adenocarcinomas, some with mucus, others without, may arise a) after cuboidal or columnar metaplasia of the surface epithelium or b) through development of Brunn's nests and glands, cystitis glandularis and formation of true glands which contain mucus. Mucus-containing cells and glandular structures may also appear in a predominantly transitional cell carcinoma.[31]

All three of these tumors (transitional cell carcinoma, squamous cell carcinoma and adenocarcinoma) may occur in pure form or in any combination with one another. They are all slowly growing tumors whose clinical behavior depends much more on their effect on the supporting stroma, the bladder wall, the muscularis, the vascular channels, and the urinary flow, than on their morphologic appearance.

SUMMARY

Only by an understanding of the manifold potentialities of bladder epithelium can the fundamental pathology of the epithelial tumors of bladder be comprehended. These potentialities consist of 1) an outward growth of epithelium with the formation of papillae, or an inward growth of the epithelium with the formation of Brunn's nests; 2) ability to change into squamous, columnar, or cuboidal epithelium, and to form glandular structures, some containing mucus, others without mucus but having an "enteric" appearance, and still others resembling renal tubules; and 3) ability to form epithelial tumors which may vary from transitional cell carcinoma to carcinoma in which the cells are differentiated to squamous or glandular, either in pure or mixed forms, and to carcinomas which are completely undifferentiated.

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[31] Dart, R. O.: Grading of epithelial tumors of the urinary bladder. J. Urol., **36:** 651-668, 1936.

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RADICAL CYSTECTOMY FOR ADVANCED CARCINOMA OF THE BLADDER

EMILE SAYEGH

From the American Mission Hospital, Tanta, Egypt

Two major problems are involved in the successful surgical treatment of carcinoma of the bladder: 1) the preservation of kidney function and 2) the excision of the tumor. The first has been attended by a large measure of success. The many procedures at our disposal for transplanting the ureters, and the advances in postoperative therapy, have made this part of the surgical treatment comparatively safe for the patient. The excision of the growth is still in a process of evolution. Simple cystectomy has given way to total cystectomy (namely, with prostatectomy and seminal vesiculectomy in the male, and with panhysterectomy in the female). Total cystectomy, in turn, is now coupled with extensive pelvic adenectomy—called by some "radical cystectomy."

This paper deals only with cases of advanced bladder tumor, involving more than one-fourth of the bladder, with deep infiltration of the muscularis, serosa, and perivesical spaces, and with enlarged pelvic lymph nodes. One hundred and six such cases have been reviewed; of these, 99 were males and 7 females. We have purposely omitted some 15 cases of early carcinoma (grades I and II), not involving the muscularis of the bladder, since the controversy regarding the subjecting of these patients to radical procedures is outside the scope of this paper.

From the standpoint of treatment, the cases reviewed here fall into three groups: 1) those with transplantation of the ureters only, 2) those with ureteral transplantation and total cystectomy, 3) those with ureteral transplantation, total cystectomy, and extensive lymph node dissection.

Our aim has been to determine whether any of these procedures is justified and, by a comparison of the survival rates of the three groups, to ascertain which method has given these patients the greatest measure of palliation.

END RESULTS OF THE THREE PROCEDURES USED

Group 1: Bilateral transplantation of the ureters to the rectosigmoid. Twenty-one patients were subjected to bilateral transplantation of the ureters only, for one or another of the following reasons: 1) extension of the tumor beyond the possibility of successful excision, 2) the poor condition of the patient, 3) refusal by the patient of total cystectomy because of the impotence that follows.

The survival rate in these 21 cases was as follows:

Immediate postoperative mortality	2 (9.5%)
2 to 6 months	7
6 to 12 months	9
12 to 18 months	2
18 to 24 months	1

Read at annual meeting, American Urological Association, St. Louis, Mo. May 3, 1953

There were thus no survivals after the second year.

In no case was a regression of the cancer observed. After the initial rosy period, of 2 to 6 weeks, the patients suffered greatly from the passage of tumor shreds through the urethra. It became necessary to perform interruption of the second, third, and fourth sacral nerves in 7 cases to obtain relief from this *complaint*.

Group 2: Bilateral ureteral transplantation and total cystectomy. Twenty-three patients were treated by bilateral transplantation of the ureters and total cystectomy without pelvic adenectomy, with the following results:

Immediate postoperative mortality	3 (13%)
2 to 6 months	4
6 to 12 months	11
12 to 24 months	4
32 months	1

In this group, there were no survivals after the third year. A comparison with Group 1, therefore, shows no appreciable difference in the end results of these two procedures.

Group 3: Bilateral transplantation of the ureters, total cystectomy, and pelvic adenectomy (radical cystectomy). Simultaneously with Group 2, which dates back to 1947, a parallel series of cases was treated by total cystectomy and pelvic adenectomy. In 1950, an appreciable improvement in the end results was noted from this procedure, and from then on total cystectomy without adenectomy was discarded.

Sixty-two patients were subjected to total cystectomy and extensive pelvic adenectomy, with the following survival rate:

Immediate postoperative mortality	6 (9.6%)
2 to 6 months	17
6 to 12 months	15
12 to 18 months	1
18 to 24 months	2

There were thus 21 survivors in this group. Of these, 11 were operated upon from 1 to 2 years ago; 2 from 2 to 3 years ago; 5 from 3 to 4 years ago, and 3 from 4 to 6 years ago. Granted that some of these patients may still succumb from cancer—since one, operated upon 1 year ago, has developed spinal metastases, and another, operated upon 2 years ago, has a perineal mass in the region of the posterior urethra which shows definite tumor cells—there are 8 patients (13 per cent) in this group who have survived more than 3 years, whereas no patient lived beyond this period following the other two procedures.

DISCUSSION

A comparison of the immediate postoperative mortality in the three groups shows them to be about the same (10 per cent) and it may be that this figure cannot be greatly improved upon in these advanced cases. Peritonitis is still a hazard in the transplantation of large, dilated ureters, and cardiovascular and renal complications are frequent in the elderly with any extensive procedure.

An analysis of the late causes of death has revealed some interesting facts The highest mortality rate was in the period between the first and second years, and by far the most frequent cause of death was local pelvic recurrence Accordingly, the operation protocols were studied, with the following significant findings

1) Accidental spill of tumor tissue at the time of operation occurred in 6 cases, and in all of these there was early recurrence of carcinoma in the pelvis The following are examples

Case 1 On freeing the right lateral wall of the bladder from the pelvis, the bladder was inadvertently opened Its interior was filled with soft jelly-like tumor tissue and some of this was spilled into the field In spite of a satisfactory postoperative course, the patient was seen in a dying condition at 4 months, with a rapidly growing tumor in the pelvis the size of a 6 months pregnant uterus

Case 2 The small intestine was adherent to a large infiltrating tumor of the bladder, and on freeing the intestine a spill of tumor tissue from the bladder occurred Resection of the small intestine was done, and bilateral transplantation of the ureters to the sigmoid, total cystectomy, and pelvic lymph adenectomy carried out The postoperative course was very satisfactory, nevertheless, the patient was seen in 3 months with massive infiltration of the abdominal wall and incision with recurrent carcinoma

2) Extension from the bladder growth to the endopelvic fascia, even though separating easily, consistently resulted in early local pelvic recurrence

3) In advanced carcinoma of the bladder involving the ureteral orifices, the tumor cells have been seen to involve the muscular coat of the ureter Therefore, the ureter should be sectioned well away from the bladder The following is a case in point

A tumor of the bladder involved the left ureteral orifice, with a large and dilated ureter This was transplanted to the rectosigmoid by a direct Nesbit anastomosis Cystectomy and adenectomy was carried out Two months later, a large pyonephrosis had developed on that side and nephrectomy was performed Postoperatively, there developed a persistent draining sinus from the lower end of the nephrectomy wound Abdominal exploration revealed a large tumor mass in the area of anastomosis on the left side, extending retroperitoneally Due to the presence of the right ureter just below this area, nothing could be done The patient died from intestinal obstruction Section of the ureter showed tumor cells

4) In carcinoma involving the bladder base, as previous papers have stressed, the urethra should be sectioned well away from the bladder In one of our patients, a thin subject, the usual abdomino perineal procedure had been waived aside for the easier abdominal procedure only Subsequently, there was recurrence of squamous cell carcinoma from the bladder in the posterior urethra, apparently in the region of the external sphincter

5) Total cystectomy and extensive pelvic adenectomy is extremely unsatisfactory in the obese and is accompanied by a high early postoperative mortality

6) Aortic and common iliac adenectomy cannot be satisfactorily performed if the ureters have been transplanted at a previous operation.

7) Early bone metastases were of high incidence in those who had undergone cystectomy, but were not present in the same high degree in those treated by ureteral transplantation nor in patients who had no surgery. Five instances of such metastases, occurring from 6 to 18 months postoperatively, were noted: three in the lumbar spine, one in the os pubis, and one in the sacrum. These cases showed no malignant changes in the removed prostates, and it seems reasonable to implicate the venous drainage of the bladder in the spread of the cancer cells. This is especially so when, during cystectomy, the bladder is manipulated and tumor cell emboli in the vascular spaces milked and sent on their way.

In a few cases, during operation, temporary ligatures were placed on both common iliac veins, the hypogastric or internal iliac arteries on both sides were cut between ligatures, and the internal iliac veins were exposed and cut between ligatures. Diodrast was injected into the distal end of the internal iliac vein and x-rays taken. In a surprising number of cases the dye was seen in the vertebral veins, thus confirming the work of Batson and Norgore.

Accordingly, in the last 17 cases of group 3, all vascular connections of the bladder were carefully severed, both abdominally and perineally, *before the bladder was manipulated.* Although it is still too early to determine the results of this procedure, thus far—in a period of a year—no bony metastases have been observed.

8) Of the 95 patients who survived the difficult operative procedures, 4 died of renal failure and 3 of undetermined causes.

At the present time, the high operative mortality rate and the not too encouraging late results should make one question the justification of asking a patient to submit to such heroic procedures. Theoretically, wide and complete radical excision should offer the best hope of a cure. However, a good percentage of cases, on operation, show extension of the tumor beyond the possible limit of surgical excision, and this percentage, when added to the immediate operative mortality, makes a considerable mortality rate that probably cannot be improved upon.

On the other hand, in a large percentage of cases cancer of the bladder does remain localized for a certain period in the pelvis. And if, in the male, our 5-year survival rates are poor, this is because in this difficult situation our methods, and indications and contraindications, have not been standardized. In the female, in whom cystectomy is easier and more radical because of the possibility of doing a panhysterectomy at the same time, the results have been consistently better. In fact, of 7 advanced cases operated upon in this way, 3 are still alive 3 years or more after surgery.

The gynecologists have worked out the exact pathways of lymphatic spread in cancer of the uterus. Their results are better than ours. Also, further studies must be done to determine the possibility of venous spread to the vertebra, to the liver, and through the plexus of Santorini to the endopelvic fascia and the pelvis Until this is done, our surgical procedures will yield poor 5-year survival rates

SUMMARY AND CONCLUSIONS

One hundred and six cases of advanced carcinoma of the bladder (99 males and 7 females) have been reviewed, with the object of determining which of three surgical procedures employed offers these patients the greatest measure of palliation

These three procedures are 1) bilateral transplantation of the ureters to the rectosigmoid only, 2) ureteral transplantation and total cystectomy (namely, with prostatectomy and seminal vesiculectomy in the male, and with panhysterectomy in the female), 3) total cystectomy with extensive pelvic adenectomy (radical cystectomy)

The immediate postoperative mortality rate was about the same (approximately 10 per cent) in the three groups

In the first two groups, there were no survivals beyond the third year

In the third group—radical cystectomy—8 patients (13 per cent) have survived more than 3 years, of these, 3 were operated upon from 4 to 6 years ago, with no signs of recurrence

The late causes of death are analyzed and the major ones discussed By far the most frequent cause was local pelvic recurrence

The possibility of the spread of cancer cells through the vascular channels at the time of operation is considered

From our results in this series of cases, it is concluded

1) That bilateral transplantation of the ureters alone is unsatisfactory

2) That bilateral ureteral transplantation with total cystectomy has shown little better results

3) That total cystectomy with extensive pelvic adenectomy has given the best palliative results More than that, in a few cases there has apparently been complete extirpation of the growth

4) It is our belief that this is the operation of choice, and should be the standard procedure for the early case

I am indebted to the constant advice and encouragement of Dr H S Hutchison, Director of the American Mission Hospital, Tanta, Egypt, to Dr Philip Sahyoun, Professor of Pathology, American University of Beyreuth, to Dr Paul Hamilton, Pathologist, Naval Research Unit No 3, Cairo, Egypt, to the United Presbyterian Church of North America, which supplied the necessary funds for this study, and to the resident staff and nurses of the American Mission Hospital, whose constant vigilance and endeavor made this work possible

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SECONDARY TUMORS OF THE PENIS

MORTON C WILSON, GEORGE R HORTON AND BILL F HORTON

From Department of Urology, Kings County Division Kings County Hospital, Brooklyn 3, N Y

The penis is an infrequent site for metastasis Secondary invasion is rare even when an advanced primary growth is situated in a nearby organ Wattenberg collected 19 cases of secondary tumors of the penis from the literature and added a case of his own His statistics are summarized in table 1 We have collected ten new cases of secondary neoplasms of the penis which have occurred since the appearance of Wattenberg's paper in 1944 and one case not included in the original statistics (tables 2 and 3)

Wattenberg, citing Chauvin, mentions a few cases of sarcoma arising elsewhere in the body and secondarily involving the penis To the total we wish to add the thirty second case of secondary carcinoma of the penis and the sixth arising in the prostate

CASE REPORT

A 53 year old Jewish baker was admitted to Kings County Hospital on June 25, 1952 complaining of back pain and difficulty in voiding His symptoms dated back to May 1949, when a prostatectomy advised elsewhere was refused by the patient One month later orchiectomy was performed at still another hospital The patient was relatively asymptomatic until 3 months prior to the present admission when he was admitted to the Coney Island Hospital with a history of urinary retention for 2 days prior to admission A transurethral resection was performed at this institution The pathological report was adeno carcinoma of the prostate The slides of the original tissue were reviewed by Dr Gherardo Gherardi "Microscopic examination of the fragments of prostatic tissue obtained reveals widespread invasion and replacement by nests, cords and small sheets of rather anaplastic tumor cells Most of these are irregularly polygonal, have an abundant pale clear cytoplasm and single plump vesicular nuclei exhibiting varying degrees of hyperchromatism, bizarreness of shape and prominence of nucleoli Here and there is a tendency for the cells to be cuboidal and arranged around central lumina In some areas tumor cell clumps are noted in the perivascular locations and rarely within the lumina of venules The stroma contains scattered and focal collections of chronic inflammatory cells" (fig 1, *A* and *B*)

The patient did poorly following operation complaining of dysuria and low back pain radiating down both legs Weight loss, anorexia and weakness were progressive up to the present admission

Physical examination revealed a markedly cachectic white man appearing chronically ill The significant physical findings were a prostate which was normal in size but stony hard, nodular and asymmetrical, two plus pitting edema of the left leg and an absence of both testicles The penis appeared normal but on palpation both corpora cavernosa were infiltrated by irregular bands of

TABLE 1

PRIMARY SITE	NUMBER OF CASES
Bladder	5
Prostate	4
Kidney	3
Rectum	3
Testicle	3
Liver	1
Lung	1
Total Primary Sites: 7	Total Cases: 20

TABLE 2

DATE	AUTHOR	PRIMARY SITE
1929	Nogues	Prostate
1947	Musiani	Bladder
1948	Burrell	Kidney
1949	Markson et al.	Nasopharynx
1950	Thompson	Rectum
1951	Cattell and Mace	Rectum
1951	Fort et al.	Bladder
1952	Boyd	Rectum
1952	Boyd	Rectum
1952	Garlick	Lung
1952	Garlick	Lung

TABLE 3

PRIMARY SITE	NUMBER OF CASES
Bladder	7
Rectum	7
Prostate	6
Kidney	4
Lung	3
Testicle	3
Liver	1
Nasopharynx	1
Total Primary Sites: 8	Total Cases: 32

hard, nodular tissue approximately two cm. in width and extending along the entire shaft of the penis from the base almost to the corona. The glans, urethra and corpus spongiosum were not involved.

Laboratory studies were as follows: Urea 50 and 60 mg. per cent on two determinations, sugar 69 mg. per cent, acid phosphatase 1.4 Bodansky units and a negative blood serology (Mazzini).

The electrocardiogram was normal and the chest film showed a diffuse bronchopneumonic process. X-ray studies of the skull and long bones showed no abnormalities.

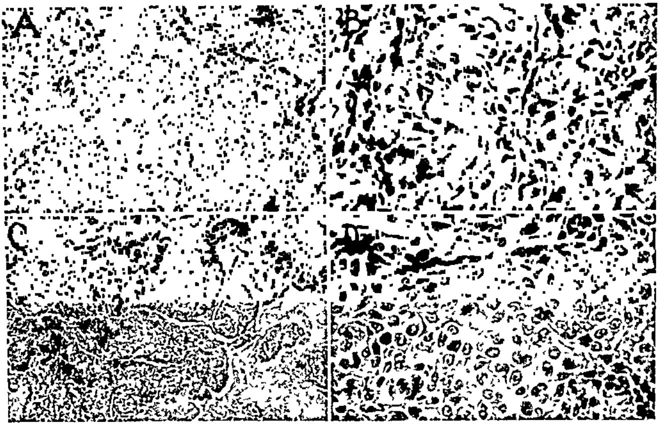

FIG. 1. *A* and *B*, original carcinoma of prostate. Section is from fragment removed by transurethral resection. *A*, ×40 *B*, ×250. (Courtesy of Dr. Harold Fink, pathologist, Coney Island Hospital, Brooklyn, N. Y.) *C* and *D*, biopsy taken from metastatic mass in left corpus cavernosum. *C*, ×40. *D*, ×250.

The urinary residual on admission was 110 cc. Cystoscopy was performed with difficulty. The bladder mucosa showed evidence of a marked cystitis and the prostate appeared markedly irregular with a complete absence of the normal landmarks and large quantities of sloughing tissue. The penile urethra appeared normal throughout. A biopsy was taken from the left corpus cavernosum.

The microscopic examination of the biopsied tissue was described by Dr. Gherardi as showing "morphological characteristics essentially similar to those observed in the previously obtained prostatic tissue. The tumor shows greater dedifferentiation and there is only a rare suggestion of gland formation. The cells are arranged in medium-sized rounded nests, in pavement fashion, or small whorls, or dissociated. Some of the cells have a somewhat pink cytoplasm. Necrosis is also in evidence. Diagnosis: Anaplastic carcinoma, probably metastatic from the prostate" (fig. 1, *C* and *D*).

The patient pursued a rapidly down-hill course characterized by temperature elevations up to 103F, extreme weakness and severe dysuria. Death occurred on the sixteenth hospital day. Permission for a postmortem examination could not be obtained.

DISCUSSION

Musiani attributes the rarity of metastasis to the penis to the nature of the blood supply to the penis which is not derived from one of the major vessels of the body but from tributaries which are not major participants in the vascular supply. Also, the repeated washings of the cavernous spaces by the influx and outflowing of blood in erection and detumescence make it difficult for tumor emboli to implant here.

Secondary tumors of the penis most commonly involve the corpora cavernosa usually, but not always, sparing the glans, urethra and corpus spongiosum. The lesions are generally nodular and circumscribed but may be diffuse involving the penis extensively. If the glans is involved, the lesion appears as a firm, nontender nodule with or without ulceration. In the case reported by Markson et al. the tumor resembled a chancre. The involvement results either from hematogenous spread or direct extension from the bladder or prostate. Carcinoma of the prostate may invade the wall of the membranous urethra via the lymphatics progressively invading the bulb and erectile tissue of the corpora eventually to involve the entire extent of the penis filling the sinuses of the erectile tissue with tumor cells. This is due to the ample communication of the sinuses with each other and those of the opposite side through fissures in the fibrous septum of the tunica albuginea. Thompson believes that a primary in the rectum may invade the corpus cavernosum by direct extension by way of the ischiorectal fossa through the junction of the deep and superficial triangular ligaments with Colles' fascia into the superficial perineal space. Involvement of the corpus spongiosum would be through the urogenital diaphragm, since cancer cells usually do not spread against fascial planes. Boyd believes a more logical explanation would be lymphatic spread downward into the perineal region via the inferior hemorrhoidal lymphatics and then by lymphatics following the course of the inferior hemorrhoidal and internal pudendal veins. The spread would by by lymphatics accompanying the internal pudendal vessels which supply the penis and ischiocavernosus muscle. Venous metastasis would be unusual since the venous drainage of the rectum is away from the penis.

Symptoms are of two types: 1) priapism due to blockage of the cavernous spaces of the corpora by tumor tissue, secondary stasis and thrombosis of the uninvolved sinuses and 2) disturbance of the urinary function due to encroachment on the urethra. Priapism may occur in any penile tumor but according to Boyd is most common in metastatic lesions.

Most of the reported cases terminated fatally a short time after the penis became involved. Cattell's case of a secondary occurring in the penis 2½ years after an abdominoperineal resection was done was alive 9 years after a local excision of the penile metastasis. In Boyd's case the penile metastasis from the rectum occurred 5 years after abdominoperineal resection. Local excision of the metastatic mass was followed 10 months later by total penectemy for a metastasis within one corpus cavernosum. The patient was alive and well 7½ years after removal of the primary in the rectum.

SUMMARY

The literature of secondary tumors of the penis is reviewed and an additional case with the primary in the prostate is reported.

Holt-Krock Clinic, Fort Smith, Ark. (M.C.W.)
10 Schermerhorn Street, Brooklyn, N. Y. (G.R.H.)
10 Schermerhorn Street, Brooklyn, N. Y. (B.F.H.)

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SOME OBSERVATIONS ON THE CRYPTORCHID TESTIS

JOHN N. ROBINSON AND EARL T. ENGLE

From the Squier Urological Clinic, Presbyterian Hospital, College of Physicians and Surgeons, Columbia University, New York, N. Y.

The intrinsic nature of the cryptorchid and its management is an ever present problem of the urologist. This subject has been an object of constant study in this clinic since one of us first showed, more than twenty years ago that chorionic gonadotropins would cause testis descent in immature rhesus monkeys.[1]

This observation was followed by widespread use of gonadotrophins and other hormones in the clinical management of cryptorchidism. There is agreement that about 20 per cent of cases treated show good result with the attainment of scrotal position.

Perhaps there is more difference of opinion and of practice as to the proper age at which hormone therapy should be given, or where a resort to surgical measures be taken than in any other aspect of this problem.

Colby[2] states that 86 per cent of all testes are normally descended at birth; 14 per cent are not, but the majority of these will come down in the first year of life. Deming[3] estimates that only 1 per cent are undescended at birth, but regardless of how many fail to descend, there is agreement that only one in five hundred will remain in an abnormal position after puberty. It is generally conceded that the development of the testis can be divided into five definite stages:[4, 5] From origin to birth, when it is receiving maternal hormones from the mother; from birth to the age of four or five years when the testis is static; from six to ten when the testis is growing; from eleven to fifteen while maturity occurs; and from sixteen through complete maturity.

For this study over 150 testicular biopsies have been taken either at the time of orchiopexy or following orchiopexy. In a few instances the whole testis was removed and studied either because the testis was apparently worthless or the cord was so short that the testis could in no manner be replaced. Excluded from this study are those cryptorchid testes which did not need surgery and those which would come down by themselves or those that came down with the aid of chorionic gonadotropins. All those with endocrine disease were also excluded. About one quarter of these cases had a course of gonadotropic hormones some time previously. This did not seem to make any difference in the pathological findings as a careful study of the cases which received the hormones and those that did not revealed no difference.

Read at annual [illegible] Urological Association, St. Louis, Mo. May 13, 1953.

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TABLE 1

	Group I
	Birth to 5 or 6 (66m)
Seminiferous tubules	1. Small
	2. Lined with layer of ovoid or cuboidal cells
	3. Occasional spermatogonia
Stroma	1. Abundant and fibroblastic
	Group II
	5–10 years (85m)
Seminiferous tubules	1. More tortuosity and coiling
	2. Several layers of cells
	3. Increasing number of spermatogonia
	4. Lumens
Stroma	1. Fewer fibroblasts
	Group III
	11–15 years (114m)
Seminiferous tubules	1. Larger and contorted
	2. Active spermatogenesis
	3. Only few spermatozoa
Stroma	1. Leydig cells beginning
	Group IV
	15 years and older (115m up)
Seminiferous tubules	1. Normal spermatogenesis
Stroma	1. Abundant Leydig cells

TABLE 2. *Biopsy of 111 undescended testes*

SEMINIFEROUS TUBULES					GROUPS				
Age	Size Microns								
	150	114	85	66	I	II	III	IV	Total
Up to 5				8	8				8
6–10				26	22	4			26
11–15	2	5	10	10	10	12	3	2	27
16	8	21	16	5	5	35	7	3	50
Total	10	26	26	49	45	51	10	5	111

TABLE 3. *Biopsy of 20 unilateral testes following orchiopexy*

1. Average age at time of orchiopexy: 10
2. Average years elapsed from operation to biopsy: 9
3. Condition of testes:
    - 15 tubular fibrosis
    - 4 abnormal testes
    - 1 normal

It has proved very difficult to classify cryptorchids by any method of grouping. In order that it may be shown how these testes differ from each other and from the normal testes, a table has been made which in some ways is similar to that described by Charney. His grouping for normal testes has not been followed exactly because in our experience there are some differences in interpretation and in the size of the seminiferous tubules.

TABLE 4. *Comparison of 42 testis biopsies (cryptorchid and normal in same child)*

AGE	NO. OF CASES	DIAMETER TUBULE, MICRONS		GROUP	
		Crypt	Normal Descent	Crypt	Normal Descent
5	4	38	38	I	I
6–10	4	60	85	I	II
11–15	8	93	150	II	III–IV
16–	5	114	180	II	III–IV

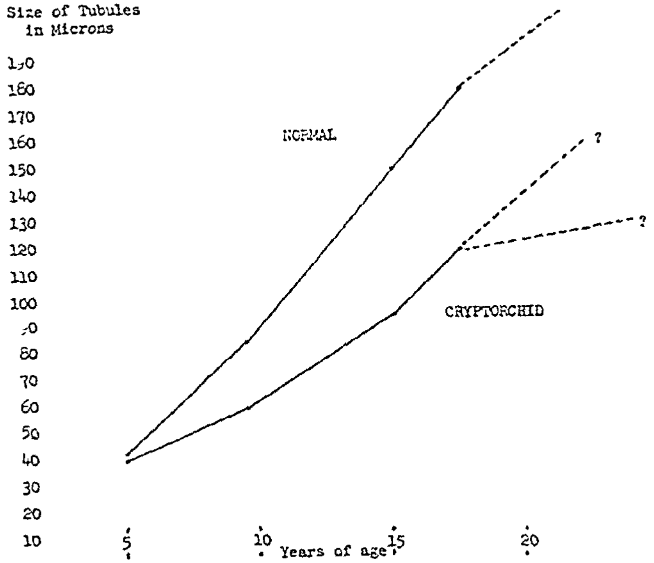


FIG. 1. Graph showing difference in size of seminiferous tubules at different age groups.

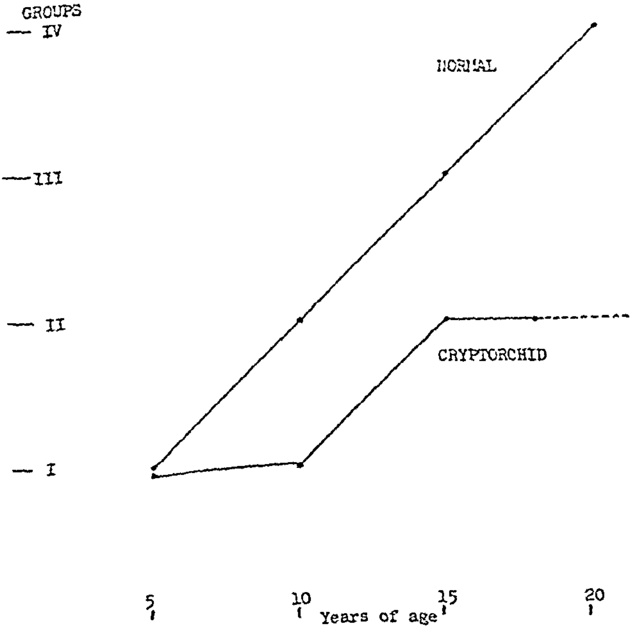


FIG. 2. Graph showing 1) steady growth of normal testis and 2) delayed growth of cryptorchid testis and age when it is delayed most.

Table 1 represents a normal guide to growth of the normal testes. Table 2 represents 111 cases of testicular biopsies which were taken at various ages from 5 years through 50 On the left of the table is represented the size in microns of the seminiferous tubules. On the right the testicles are classified according to the groups which have been classified in table 1 It will be noted that up to the age of 5 all of our 8 cases fall into the group where the diameter of the seminif-

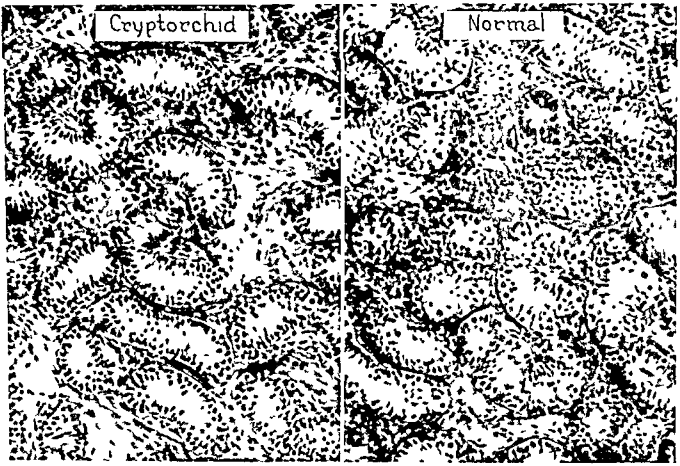


FIG 3 Case 1 Patient aged 5 years Few changes are to be noted between two sections

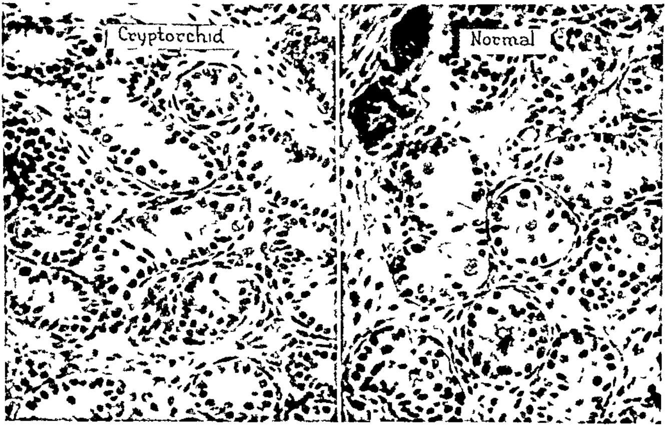
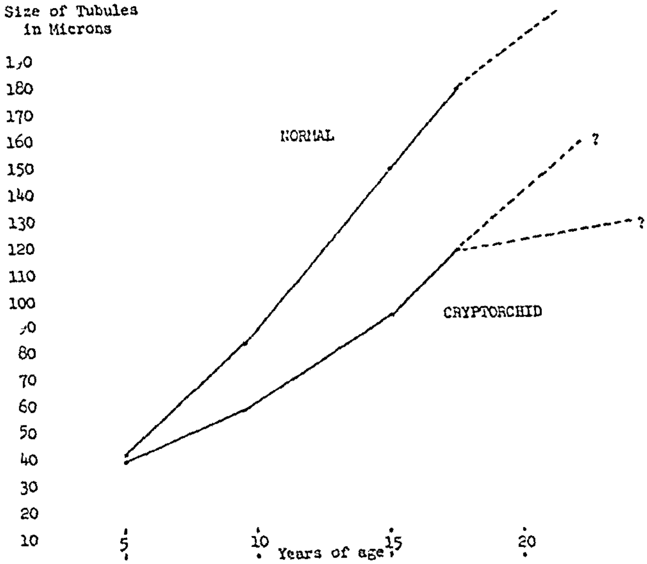


FIG 4 Case 2 Patient aged 5 years Both sections similar

TABLE 4. *Comparison of 42 testis biopsies (cryptorchid and normal in same child)*

AGE	NO. OF CASES	DIAMETER TUBULE, MICRONS		GROUP	
		Crypt	Normal Descent	Crypt	Normal Descent
5	4	38	38	I	I
6–10	4	60	85	I	II
11–15	8	93	150	II	III–IV
16–	5	114	180	II	III–IV



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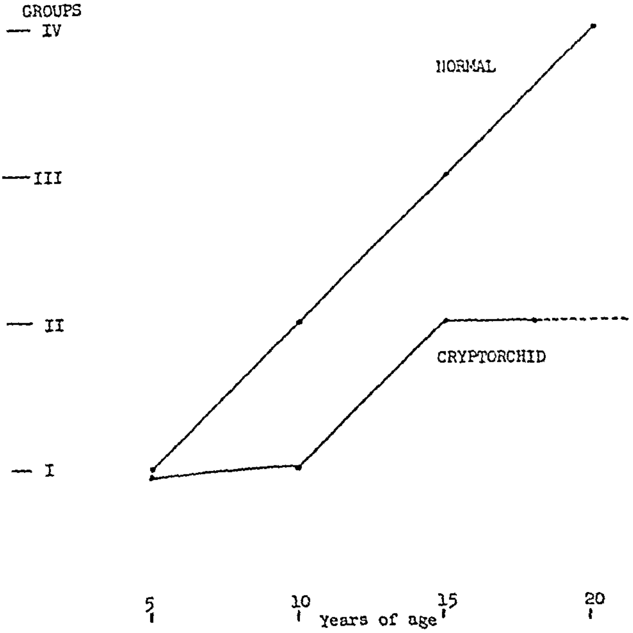

FIG. 2. Graph showing 1) steady growth of normal testis and 2) delayed growth of cryptorchid testis and age when it is delayed most.

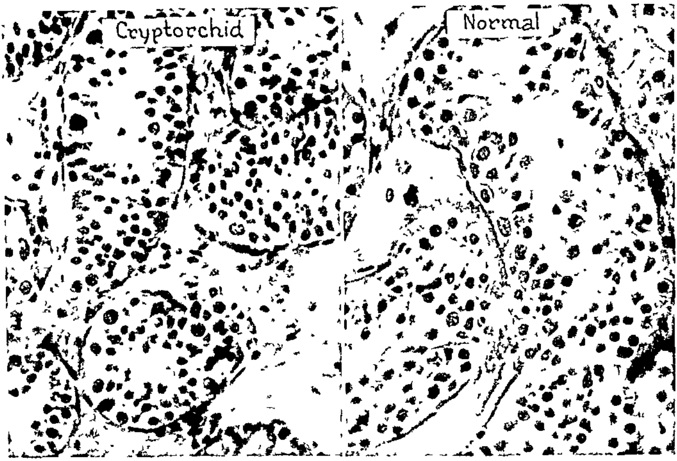

FIG. 6. Case 4. Patient aged 11 years

there are still 5 that fall into the classification of 5 years or under. The really striking fact to note in table 2 is that there are only 3 undescended testes after the age of 16 which appear microscopically normal.

The second series of 20 testicular biopsies had previous orchiopexies, and were studied for sterility diagnosis. Table 3 shows briefly the average age at the time of operation, the number of years elapsed since operation, and the condition of these testes. The striking fact is that of this group there was only one completely normal testis. These findings have been confirmed by others.[6]

A summary of the third series of 42 testicular biopsies which were taken from unilateral undescended and normally descended testes in the same child during the same operation is presented in table 4. It can be seen from a study of this chart that up to the age of 5 there are no really gross differences either in the size of the tubules or into the group which they fall. From 6 to 10 it can be easily seen that there is now beginning to be an increase in the size of the seminiferous tubules and also there are beginning to be other changes associated with growth. From 11 to 15 there is even more marked difference in the size of the seminiferous tubules and the normally descended testicle is beginning to show signs of spermatogenesis while the cryptorchid shows only a few developmental changes. Over age 16 the difference in the tubules is more marked. The cryptorchid testis is growing but its rate of growth is much less than in the normally descended one. The cryptorchid testicle still shows no evidence of spermatogenesis while normal ones still show marked evidence of spermatogenesis.

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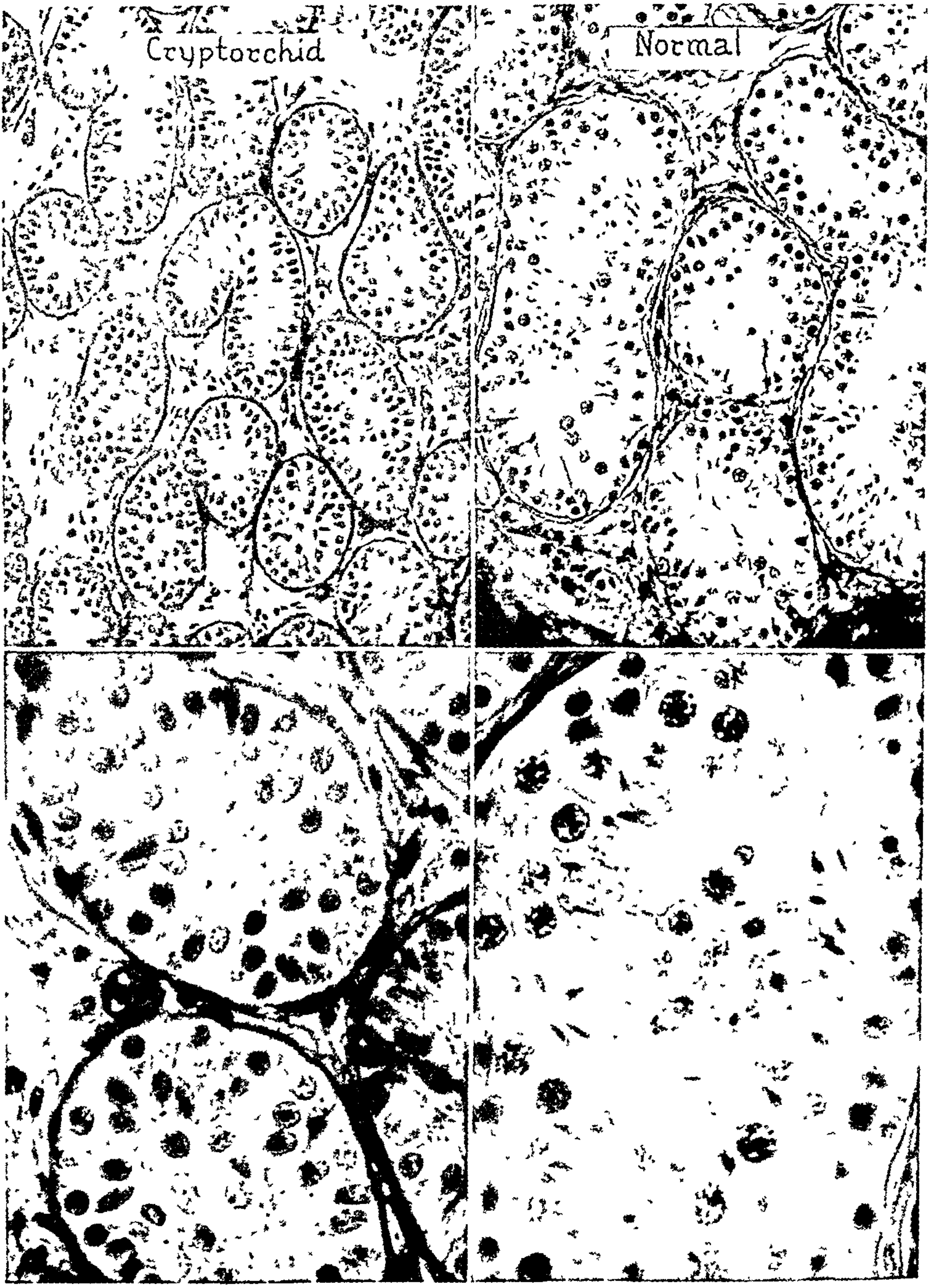

FIG. 7. Case 5. Note marked difference in two sides

Figures 1 and 2 show graphs representing a comparison of size of seminiferous tubules and age.

From many biopsies we have chosen the following photomicrographs (fig. 3, aged 5 years; fig. 4, aged 5 years; fig. 5, aged 10 years; fig. 6, aged 11 years; fig. 7, aged 15 years) to illustrate our findings. They are arranged so that you may compare the normally descended testes with the cryptorchid testes. They are taken at low and high power magnifications which are sufficient to show the changes which occur in the testicles

DISCUSSION

There are certain obvious facts from which recommendations may be made that should be of value to all, in the care and treatment of the cryptorchid testis

A careful evaluation of these biopsies shows that prior to 5 years of age the cryptorchid testis keeps relative pace with the normally descended one In the next period of growth it shows retardation in development as compared to one in its normal position[7] During puberty it continues to grow but rarely becomes normal After orchiopexy, done just prior to, or at the time of puberty, only a few testes will develop properly It is also seen from our other series that a cryptorchid testis that does not descend by the time of, or after puberty, will in the majority of cases show no fertility potential A testis left in the intra abdominal position through nondescent or operative procedures has a definite predisposition to develop cancer Baker[8] states that the incidence of cancer in the normal testes is 0 0013 per cent, and the incidence of cancer in undescended testes is 11 per cent The incidence of cryptorchidism in 7000 patients with cancer of the testis is 10 9 per cent One should also consider that inguinal testes are readily subject to trauma

In view of our findings it is suggested that all children with unilateral or bilateral undescended testes not due to endocrine disturbances should be treated before the age of five years Although a certain number of these testes have an inherent congenital defect it is wise to give each testis every chance to develop by being placed in the scrotum before any growth occurs There are testes grossly small that show complete absence (germinal aplasia) of all spermatogenic elements These, if unilateral, should be removed

The first step in treatment consists of hormonal injections The authors and others[9] suggest that larger doses of gonadotropins should be given over a shorter period of time rather than smaller doses over a longer period of time thus preventing precocious sexual development or bone changes Recently we have been trying 4000 to 5000 units of chorionic gonadotropin daily for three days, and if there is no change within a week, operation is recommended The first seven cases showed the following findings 1) failure due to lack of an external ring, 2) success, 3) failure due to absent testicle, 4) failure due to a very small external ring and herniae, 5) success, 6) failure due to the testis adhering to the fascia above and outside the external ring, 7) success

Many different types of operation have been recommended for replacement of the testis in the scrotum As long as the following principles are followed, the exact type of operation is not too important 1) The spermatic cord must be of sufficient length to allow the testis to be placed in the scrotum without tension

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[8] Baker, R C Discussion of cryptorchidism Fertility & Sterility, 3. 476, 1953
[9] Heller, C G and associates Personal communication
[10] Kiefer, J H Surgical treatment of cryptorchidism J Urol , 68: 385, 1952

2) There must remain an adequate blood supply to the testis. 3) The tests must be located in the scrotum with as little tension as possible, and to achieve this, at times the cord must be carefully stripped of all cremasteric bands and the vessels mobilized up to their origin at the aorta. 4) There must be some form of fixation of the testis to the scrotum and from the scrotum to the leg either by suture or by elastic tension for a period of time. Use of permanent fixation to the thigh if there is any doubt of proper replacement of the testis or poor blood supply. If the testis can be placed normally in the scrotum without tension certainly various forms of external elastic tension are sufficient. The closure is well standardized.

Small testes which cannot be placed normally in the scrotum should not be left in the abdomen. Occasionally they can be left in the groin where they can be watched and either removed or brought down later. If the cord is so short as to preclude the former, they should be removed, primarily because they will not become fertile and because of the danger that they will become neoplastic.

SUMMARY AND CONCLUSIONS

In these three series of 173 testicular biopsies it is interesting to note that in only a very few instances is the cryptorchid testis completely normal as compared with the normally descended one at any period of time during its growth. It comes closest to being normal before the age of 5 years. Still recognizing that we cannot rule out the fact that certain of these testes may be born with an inherent defect which will also prevent their development, it is believed that it is wiser to replace cryptorchid testes in the scrotum before the period of growth takes place. In this way they will be given every opportunity to get the maximum amount of development that is possible during normal growth. It is realized that probably some of these testes will be sacrificed because of the difficulty of surgery in this age group, but we believe that this is far more satisfactory than to leave an inherent or a defective testis still present in an abnormal position. Certainly no harm results if all these children between the age of 2 and 5 receive large doses of hormones over a short period of time, as previously recommended. If there is no result within one week, operation is recommended at this time.

180 Fort Washington Ave., New York 32, N. Y.

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THE CRYPTORCHID PROBLEM

J S GROVE

In 1851 Le Comte stated that the undescended testis frequently becomes malignant, and since that time this subject had had numerous confusing reports Wangensteen[1] in 1927 wrote "no greater diversity of opinion probably exists concerning anything in medicine than the question of malignancy in the undescended testis " The question of what to do with the undescended testis varies from immediate removal to no therapy at all Those who believe in the high incidence of malignancy in these testes advise orchiectomy, while others like Charny et al ,[2] believe that the undescended testis is an abnormal one i e , has constitutional defects at the time of its formation, and from the standpoint of fertility that this testis, even if brought down at an early age, will be of no functional value, and therefore had best be left alone

As to the incidence of malignancy in cryptorchids, Campbell[3] in 1942 said "it can be unequivocally stated that the undescended testis is more liable to malignant changes than the normally placed testis, and that the abdominal one is more liable to malignant changes than the inguinal " From a purely statistical standpoint Campbell had figured that 1 abdominal testicle out of 20 undergoes malignant changes, and that 1 inguinal testicle out of about 80 undergoes malignant changes Taken together there were about 2 malignant growths to about 100 undescended testes He collected 1422 cases of malignancy in testes, and of these 165 (or 11 6 per cent) of the patients were cryptorchids

Gilbert and Hamilton[4] collected 7000 cases of tumors of the testes, and over 840 (over 11 per cent) of the patients were cryptorchids

In general the incidence of malignant cryptorchidism in relation to testicular malignancies has been given as from 8 to 15 per cent

Now as to the opposite side of this question, Carroll[5] in 1949 sent a questionnaire to members of the American Urological Association apropos the subject of malignancy in cryptorchids, and after receiving replies from 662 members (76 per cent of whom had never seen a case of tumor formation in a cryptorchid), came to the following conclusions 1) Malignant testicular tumors are rare *per se* 2) Malignancy in cryptorchidism is still more rare 3) Present statistics proving the higher incidence of malignancy in cryptorchidism cannot be accepted 4) Any urologist will be fortunate to see or treat a single case in his life span of practice 5) The incidence of malignancy in cryptorchidism from the actual cases reported is so minute that the potentiality of its malignancy cannot be used as an indication for either orchiopexy or orchiectomy

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Presidential address, read at the annual meeting of the Chicago Urological Society, April 23, 1953

[1] Wangensteen O H Arch Surg , 14 663 731 1927

[2] Charny, C W , Conston, A S and Meranze, D R Fertility and Sterility, 3 461–476, 1952

[3] Campbell, H E Arch Surg 44 353–369 1942

[4] Gilbert, J B and Hamilton, J B Surg Gynec & Obst , 71. 731–743, 1940

[5] Carroll, W A J Urol , 61. 396–404, 1949

From the foregoing, we have two schools of thought: those who believe that malignancy develops frequently enough, so that surgery should be resorted to i.e., orchiectomy; and the other group who question the advisability of any form of treatment or at most orchiopexy.

Now what about the incidence of malignancy in a cryptorchid testis which has been surgically corrected. Gilbert and Hamilton[4] in 1940 after reviewing the literature found 77 patients in whom malignant tumors developed after orchiopexy. Fourteen cases were reported of testes placed in the abdomen, which originally were located in the groin, and could not be brought down into the scrotum. Rusche[6] recently collected 4 cases where an orchiopexy had been performed with no clinical evidence of tumor at the time of surgery, and these patients later developed malignant tumors. He raised the question of the validity of the argument of carrying out orchiopexy in undescended testes as a prophylactic measure to avoid malignancy. Later in my report I shall give the history of such a case. Gordon-Taylor,[7] on the other hand, said that in view of the frequency of surgery for ectopia, the relative paucity of cases of malignant disease in testes brought into the scrotum would appear to offer some protective agency against malignancy, provided the operation is successfully performed. If this cannot be done then he advises orchiectomy. Recently Kaplan and Roswit[8] reported a case in which malignant changes took place in bilateral ectopic testes brought into the scrotum at 14 years of age. Some 27 years later malignant changes took place in one testis, and 4 years after this tumor changes occurred in the other testis. Testicular malignancy after orchiopexy has been conjectured as being due to surgical manipulation or hormonal overstimulation of a testis attempting after liberation to obtain the status of a normal organ. However, biopsy studies have shown that these testes rarely become normal organs from a germinal cell structure standpoint. They are abnormal organs to start with.

Ectopy per se has not been proved to be causative of malignancy and, therefore, it is illogical to expect that any particular site of ectopy promotes carcinogenesis, unless the factor of differences in temperature in the abdomen and groin play a part. Likewise the factor of trauma to an inguinal testis is questionable. The proportion of inguinal to abdominal testis is about 4 to 1, therefore, there would be a greater opportunity for inguinal than abdominal tumor.

Another interesting phase of this problem is that in one report,[4] tumors in normally descended testes had occurred in 23 men whose other testis was ectopic, but did not undergo any change. Rusche[6] also recently reported 4 similar cases. This illustrates the caution that must be observed in drawing any conclusions that ectopy itself is the cause of tumor formation.

Up to this point my remarks have dealt with cryptorchidism and malignancy. Let us now discuss fertility in the ectopic testis. Those of you who attended the January 1953 meeting of our society, at which time Dr. Warren Nelson excellently presented the histologic changes which occur in ectopic testis after the age of 6 years, were impressed with the sharp decrease in germinal elements in contrast to the normally placed testis. Prior to that age the changes were insignificant Recently Charny et al[2] made a critical histologic study of pre- and postoperative cryptorchids, and stated that these studies leave him with little enthusiasm for any of the surgical techniques employed Biopsies showed definite deterioration of the seminiferous epithelium after surgery in the majority of instances He believes that the ectopic testis is an inherently abnormal organ He does not advise surgery for the ectopic testis I feel that if we are to do anything about preserving chances for a fertile organ, then surgery ought to be performed much earlier than we have been advising At one time the majority of surgeons waited until the period of puberty, and if the testis did not descend at that time then surgery was advised Then with the advent of pituitary hormonal substances, these were given at 6–7 years of age, to see if the nondescent was due to insufficient hormonal stimulation, and if nothing occurred then surgery was advocated I feel that there is very little to gain from this mode of attack, provided the patient shows no other evidence of hormonal disturbance If one testis is in the scrotum then certainly there must have been enough hormonal substance in the body to do this, and if the other testis did not come down then something else is responsible for its nondescent Now that such sharp histological changes have been shown to take place about the age of 6 years, I think it would be advisable to operate on these children at a much younger age i e, 3–4 years of age

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[6] Rusche, Carl: J. Urol., 68: 340–353, 1952.
[7] Gordon-Taylor, G. and Wyndham, N. R.: Brit. J. Surg., 35: 6–17, 1947.
[8] Kaplan, G. and Roswit, B.: J.A.M.A., 144: 1557–1558, 1950.

From a general statistical study of our problem, it can be stated that tumors of the normally placed testis are rare (about 0 05 per cent) in male patients as a whole, and about 0 58 per cent of all malignant tumors Hence no individual or hospital is ever going to accumulate a great series of cases Statistics of course can be "juggled" to one's mood In regard to this study several factors for error enter 1) Most hospitals do not differentiate male and female admissions 2) Many patients are admitted more than once a year, and therefore included in total admissions, so that anywhere from 15–20 per cent of total admissions are readmissions 3) Hospital records show pathological diagnoses and not anatomical changes, therefore, many patients entering the hospital for other ailments may have ectopic testes as a coincidental finding, and therefore, this would not appear on the record, but would only show if they entered for surgery of ectopic testis Statistics, therefore, are way off in regard to the incidence of ectopic testes Accumulation of many reports show that about 10 per cent of all males are born with undescended testis, that by puberty this decreases to 2 per cent, and that by the age of 20 years to 0 2 per cent However, the manner of keeping hospital records, as previously discussed, would alter greatly the incidence of ectopic testes In other words, I believe that the frequency is higher than stated

A study was made of malignant testicular tumors at Michael Reese Hospital from 1921 to 1951, and during this period of 30 years there were 55 cases of tumors in scrotal testes, and 2 cases in ectopic testes One of these cases occurred in an abdominal testis, while the other was in a recently operated inguinal testis, which had been brought down successfully into the scrotum For this group of cases a percentage of 3 6 existed This is certainly under the figures of 10–15 per cent of malignancy in undescended testes that has been given in many reports

The first case was in a boy 15 years of age, who entered the hospital for operation on a right ectopic testis, which was situated in the groin. The left testis was normally situated. At surgery the right testis was easily brought down and the hernia, which was present, repaired. The testis showed no gross abnormal findings. A modified Bevan operation was performed. Three months later he developed severe pain in the right knee, which traveled up the thigh into the scrotum. No positive findings were noted at that time. However, nine months after his discharge from the hospital he was readmitted with the findings of a hard mass just above the symphysis. Exploratory operation and biopsy revealed a hard suprapubic mass, which on section revealed metastases from an embryonal carcinoma of the testis. The right testis showed a very small lesion, which was not felt at the time of the original operation. He was given deep x-ray therapy but expired several months later.

The second case was that of a 33 year old man, who entered the hospital with a history of noting a firm mass in the right lower quadrant of the abdomen some three weeks prior to admission. At that time he had been accidentally kicked by his child in the abdomen, and a few days later had noted the abdominal mass. He had no other complaints. Examination revealed a left testis normally placed in the scrotum, while the right half of the sac was atrophied and did not contain a testis. A mass the size of a grapefruit was felt in the right lower quadrant. The Friedman test on the urine was negative for quantitative prolan A. At surgery a large vascular retroperitoneal tumor mass was found with a vas and structures of the cord attached to it. The mass was removed, and the pathological diagnosis was embryonal carcinoma of an abdominal testis. At that time he did not receive any postoperative x-ray therapy, and one year later was admitted with evidences of metastases to the lungs. These responded to x-ray therapy. Then one year later an abdominal mass reappeared, which again responded to deep x-ray therapy. From that time on he had numerous recurrences, and finally died 5 years after his original operation.

This case is the only one, in the hospital records, of a tumor in an abdominal testis. Whether, the history of injury was of importance is hard to say. An early diagnosis could not have been made, because the testis was situated deep in the abdomen, and only after a large mass had developed could the tumor be felt. Certainly abdominal testes should be brought down early in life if possible. If any difficulty is encountered during the surgical procedure or if it cannot be satisfactorily placed in the scrotum, then it should be removed. It certainly should never be replaced in the abdomen unless the condition is bilateral.

The foregoing two cases were not seen by urologists, but by general surgeons at the hospital.

A recent case, which I took care of, is not included in the above statistics, because the number of tumors in scrotal testes in 1952 was not available as yet at the hospital.

This man was 32 years of age, and he complained of pain and swelling in the right side of the scrotum for a period of several weeks. In his past history he had had an operation for a right undescended testis at the age of 12½ years. Fortunately, from a record standpoint, this operation had been performed at Michael Reese Hospital, so that a complete record was easily available. This record showed the following facts At 6 years of age he was suddenly seized with pain in the right groin, and this was accompanied with swelling in this region Six months later he bumped himself over this area and another attack of pain ensued At that time he was seen by a doctor, who informed the mother that the child's right testis was not in the scrotum No treatment was advised, and for the next few years he had recurrent attacks of pain in the right groin At 12½ years of age he was admitted to the hospital for surgery of the ectopic testis A fair sized right testis was found in the inguinal region associated with an indirect hernia The testis was brought down into the scrotum with relative ease and the hernia was repaired On discharge from the hospital the testis was felt well down in the scrotum Following this he had no further trouble However, some ten years later, on being examined for military service, he was told that the right testis was atrophied At this time he was 22 years of age Then some ten years later, at the age of 32, he began to note swelling and pain in the right side of the scrotum On examination an apple sized, firm, smooth mass, which did not transilluminate light, occupied the right side of the sac Removal of this mass showed it to be an embryonal carcinoma of the testis This was followed by a course of deep x-ray therapy to the abdomen

The interesting features of this case are 1) the repeated history of injury to the right groin with subsequent swelling from the age of 6 to 12 years, 2) successful orchiopexy at 12½ years of age Ten years later he was told that the right testis had atrophied, and then at 32 years of age carcinoma developed in a previously ectopic testis successfully placed in the scrotum some 20 years before If cryptorchidism with trauma *per se* were the factors in initiating the malignant process, one would certainly think that it would have occurred much sooner, rather than let a gap of some 20 years ensue Surely one swallow does not make the summer, but this case would speak against the ectopia being the major factor in producing the malignant changes in the testis

By coincidence all three of the aforementioned cases occurred in the right testis, and the pathological diagnosis was embryonal carcinoma in all

Since the paper was submitted for publication, the following case has come to the author's attention

I F, 23 years of age, had noticed a small hard mass about the right testis some 9 months ago There was no history of injury and the swelling was not painful Then two months ago there was an increase in the size of the swelling with slight scrotal pain In his past history he had the right testis, which was located in the inguinal canal, brought down successfully into the scrotum This operation was performed at 5 years of age Since that time the testis was palpable in the right side of the scrotum, and gave the patient no further trouble until he noted the swelling around the organ some 17 years later Examination at this time revealed a firm, nodular mass surrounding the right testicle The testis itself felt atrophic The left testis was of good size and consistency A diagnosis of right epididymitis was made, and the patient treated conservatively However, the swelling did not subside, so that right epididymo orchiectomy was performed The pathological diagnosis was dysgerminoma of the right testis

The case reveals a malignant testicular tumor developing some 17 years after

TABLE 1. *Michael Reese Hospital, 1943–51*

ADMISSIONS	CRYPTORCHIDS	%	MALIGNANT CRYPTORCHID	% IN RELATION TO CRYPTORCHIDS
168,058	101	0.06	1	0.9

Statistics for 31 years (1921–51)

TUMORS OF SCROTAL TESTES	MALIGNANT CRYPTORCHIDS	%
55	2	3.6

TABLE 2. *Michael Reese Hospital, 1930–50*

SURGICAL SPECIMENS EXAMINED	MALIGNANCIES	MALIGNANT SCROTAL TESTES	% OF MALIGNANCIES	MALIGNANT CRYPTORCHID	% IN RELATION TO SCROTAL TUMORS	CRYPTORCHID % OF MALIGNANCIES	AUTOPSIES	DEATHS DUE TO MALIGNANCIES	TESTES DEATHS	% OF TESTES MALIGNANT
86,313	8,246	40	0.48	1	2.5	0.01	7,725	1,349	6	0.44

a successful operation for an undescended testis. This again would speak against the ectopia as being the most important factor in testicular tumor formation.

In table 1 admissions include both male and female patients, and also readmissions during the years 1943–51. It, therefore, can be seen that the percentage of patients with ectopia would be much greater than 0.06, if the statistics were only on male patients, and also did not include readmissions. Likewise the number of cryptorchid patients would be much more than the 101 if all patients with this condition were put on the diagnosis card. Only those were recorded who entered the hospital for surgery of their ectopia. With this fact in mind, then the per cent of malignancies in relation to the number of cryptorchids would be much lower than 0.01.

In table 2 covering a period of 20 years (1930–50), the per cent of malignant cryptorchids in relation to tumors of scrotal testes was 2.5, while over a period of 30 years (1921–51), the percentage was 3.6, a much lower figure then ordinarily given.

CONCLUSIONS

Numerous excellent reports do not substantiate the high incidence of malignancy in undescended testes.

I believe that the fear of malignancy in a cryptorchid testis is not a reason for surgical intervention *per se*; i.e., orchiectomy.

In view of the excellent histological studies of Nelson and Charny, if one is to preserve the germinal forming elements then surgery should be performed early, that is, before the age of 6 years, because these elements undergo early atrophy.

The use of hormonal therapy in the cryptorchid is questionable, because if one testis is in the scrotum it signifies that enough hormonal stimulation for descent is present. The reason for nondescent in the other then must be due to mechanical factors, such as adhesions or a narrow inguinal canal or some constitutional defect of the testis. Also testes which come down by themselves at puberty or later are not true ectopic testes but represent the migratory type.

In older individuals surgery may be performed for an associated symptomatic hernia, or for psychological i e , cosmetic reasons, the testis may be brought into the scrotum But the question of future malignancy should not be the cause for surgery

Abdominal testes should be placed in a position where they can be felt If this cannot be done satisfactorily then orchiectomy should be performed, provided the condition is unilateral The inguinal testis should never be placed in the abdomen, if it cannot be brought into the scrotum

The rationale for orchiopexy must rest upon the placement of the testis where it can be observed closely Contacts with these patients should be kept for many years This will give some inkling as to the changes, which occur in these organs, particularly with regard to the questions of atrophy and malignancy

In view of the long interval of time before malignant changes took place in testes successfully placed in the scrotum, I do not believe that the ectopia should be blamed for this tumor formation This took place after many years in the majority of reported cases These should be simply classified as tumors of a scrotal testis

Undescended testes, which cannot be brought down satisfactorily at the time of surgery, should not be subjected to multiple stage operations They had best be left alone if they are in the groin, and if in the abdomen then they should be removed

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CARCINOMA OF THE PROSTATE

LT. COL. K. E. VAN BUSKIRK, USA (MC) AND COL. J. C. KIMBROUGH, USA (MC)

From the Urology Section, Walter Reed Army Hospital, Washington, D. C.

It is the purpose of this paper to present the analysis of the clinical records of 136 patients with carcinoma of the prostate treated at Walter Reed Army Hospital during the 13 year period from 1940 through 1952. The incidence, diagnosis, pathology, treatment, and follow-up results are reported. Special attention is given to the early diagnosis, the selection of patients for radical surgery, and the survival rates following each type of treatment.

INCIDENCE

The incidence of carcinoma of the prostate has increased during the past two decades. Since carcinoma of the prostate is a disease prevalent chiefly among old men, this increase has, in a great measure, been due to the fact that there are more people living longer. The population of the United States has more than doubled since 1900. A part of this growth can be attributed to the increased longevity rather than to the addition of new young stock, since the internal structure of the population is shifting toward an increasingly greater proportion of older people.

Life expectancy in 1900 was little more than 45 years, whereas in 1950 this expectancy was more than 65 years. In 1900, 4.1 per cent of the population was over 65. In 1950, 8.2 per cent was over this age. The estimated percentage for 2000 A.D. is 14 per cent[1] (table 1).

A review of these data emphasize the growing number of individuals each year with cancer of the prostate and the importance of early detection and radical treatment.

"Cancer of the prostate is the third most common type of cancer among males, exceeded only by cancer of the skin and of the alimentary tract. No very exact data are available concerning the prevalence of cancer of this or of other sites, but the prevalence studies which have been made show clearly that this is one of the most important sites for males and that the rates in the age groups from about 50 upward increase very rapidly to a point more than 15 times the all ages rate. In 1948, in the United States, 11,758 males died from cancer of the prostate; this represents 12 per cent of all cancer deaths among males in that year. It is known that not nearly all of the cancer of the prostate is diagnosed or recognized even at death. Various investigators have found occult cancer of the prostate in a considerable percentage of cases given autopsy without there having been previous knowledge of prostatic cancer. These percentages have ranged from 14 to 46 and have averaged about 24 per cent."[2]

Read at annual meeting, Mid-Atlantic Section, American Urological Association, Roanoke, Va. March 13, 1953.

[1] Velz, C. J.: Manpower prospects within the population structure. J.A.M.A., **147**: 1319–20, 1951.

[2] Baker, Roger: Studies on cancer prevention in urology, Ann. Surg., **137**: 29–34, 1953.

TABLE 1. *Cancer of prostate; age group per population*

YEAR	POPULATION	AGE OVER 45 YR	AGE OVER 65 YR
	millions	*per cent*	*per cent*
1850	23.0	12.4	2.6
1900	76.0	17.8	4.1
1950	152.0	28.4	8.2
2000*	200.0	41.0	14.0

* Forecast.

TABLE 2 *Cancer of prostate*

YEAR	PTS TR FOR		TOTAL TR	% WITH CA OF PROST.
	BPH	ca.		
1940	42	10	52	19.2
1941	49	3	52	5.7
1942	29	4	33	12.1
1943	32	4	36	11.
1944	26	4	30	13.3
1945	41	2	43	14.7
1946	50	7	57	12.3
1947	50	18	68	26.5
1948	59	14	73	19.2
1949	57	12	69	17.4
1950	98	20	118	17.
1951	72	20	92	21.75
1952	100	18	118	15.3
Total	706	136	841	16.1

During the 13 year period (table 2), 1940 through 1952, there were 705 patients treated at Walter Reed Army Hospital for benign prostatic hypertrophy and 136 for carcinoma of the prostate, an incidence of 16.1 per cent of carcinoma of the prostate. This does not include the benign prostatic hypertrophy patients treated for other diseases and who did not come to the attention of the urologist. The average age of the 136 patients was 65.8. There were two young adults—one, 17 and the other, 20 years of age. In addition to these, the youngest in this group was 43, and the oldest, 89. The average age of patients selected for radical surgery was 65.2. The youngest was 51, the oldest, 81.

ETIOLOGY

The prostate is not an endocrine gland. The secretion contains organic material and enzymes. The most important of these enzymes is acid phosphatase. The evolution of the prostate is controlled, to a great measure, by hormones elaborated by the testes. It is apparent that the testicular hormone imbalance resulting from senility is an important factor. The hormonal aspect of carcinoma of the prostate is delicately balanced and it may well be that the indiscriminate use of testosterone therapy for the so-called male menopause and other conditions has

TABLE 3. *Cancer of prostate; radical perineal prostatectomy*

YEAR	NO. CA. PTS.	NO. PTS. TR. RAD. PER. PROST.	PERCENTAGE OF TOTAL RAD. TREATMENT
			%
1940	10	1	10
1941	3	0	0
1942	4	0	0
1943	4	1	25
1944	4	2	50
1945	2	2	100
1946	7	3	42.9
1947	18	13	72.9
1948	14	9	64.3
1949	12	8	66.7
1950	20	14	70.0
1951	20	12	60.0
1952	18	9	50.0
Total	136	74	54.5

contributed to the increased incidence of carcinoma of the prostate. Testosterone therapy may have exacerbated carcinoma of the prostate which would otherwise have remained relatively quiescent.

PATHOLOGY

Adenocarcioma, the most common malignant tumor of the prostate, occurs in three types.[3] The first type is well-differentiated tumor, and occurs as extra-acinar structures lined by a single layer of cuboidal epithelium resembling senile prostatitis with metaplasia. The second, the medullary adenocarcinoma, consists of large acini filled with cancer cells forming small pseudo-acini. The third is the undifferentiated carcinoma and involves the entire gland.

There are a few epidermoid carcinomas found. These are probably derived from the transitional epithelium of the prostatic urethra.

Nodular hyperplasia of the prostate and senile prostatitis with metaplasia may simulate malignant tumors. It is probable that these lesions result from androgen imbalance and may present a malignant appearance on digital rectal examination. Senile prostatitis with metaplasia may be associated with nodular hyperplasia. When there is a question of malignancy the lesion, as far as treatment is concerned, must be considered malignant. Such tumors require radical surgery.

DIAGNOSIS

Digital rectal examination is the only procedure by which an early diagnosis can be made which, in turn, will enable a majority of the patients with carcinoma of the prostate to be cured by radical surgery. When urinary symptoms appear, only a small percentage (5 to 10 per cent) of the patients are amenable to cure by surgery. Radical surgery has been feasible in more than 54 per cent of the patients at Walter Reed Army Hospital since 1940 (table 3). In a great measure this high percentage has been due to the annual physical examination in which digital rectal palpation is required Similar results could be attained in the civilian population by the proper publicity in the lay press, emphasizing the fact that cancer of the prostate can be cured only by early diagnosis and radical surgery

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[3] Lewis, L. G.: Precancerous lesions of the prostate. Surg. Cl. of No. Amer., 6: 1777, 1950.

In the cancer detection propaganda, great attention has been given to carcinoma of the breast and other organs and there is no excuse for neglecting carcinoma of the prostate in this publicity In the Walter Reed Army Hospital series of 136 patients, digital rectal examination provided the most valuable information prior to operation In the early cases, the hard nodule was the first sign As the carcinomatous process increased in size, the hardness extended, the gland became fixed and nodular and encroached upon the membranous urethra Later, the induration involved the seminal vesicles and filled the intervesicular space

Digital rectal examination, erroneous in less than 10 per cent of the patients, was considered the most reliable diagnostic procedure X rays of the bony pelvis, lumbar vertebrae, thorax, and long bones showed metastatic lesions The perineal punch biopsy was used but was often misleading unless the tissue for examination was removed from the cancer area The diagnosis was established or confirmed by examination of the tissue removed in transurethral resection in 20 patients and was negative in two Cytologic examination was done during the past five years and was positive in a few patients Cystoscopy provided little information except in advanced cases involving the trigone Increase in the serum acid phosphatase was noted with the presence of metastatic lesions This increase was present in no other disease Androgen estimations were not helpful The symptoms, pain and urinary obstruction occurred late In two patients, the first symptom was pain from metastatic lesions Sternal or iliac biopsy may show early metastases Frozen section biopsy, made at the time of the operation, has been valuable when positive The specimen may not be from the cancer area in which case a false negative report might be rendered Perineal punch biopsy is not valuable in early cases in which the nodule is small Bone marrow biopsy (sternal or iliac crest) is positive in early metastases

Differential diagnosis is not often difficult Fibrosis, following infection, calculi, and tuberculosis may be confusing Sarcoma is rare and may require a biopsy for final diagnosis These tumors, however, are usually larger, softer, and occur in younger men Granuloma of the prostate, of undetermined origin, has been mistaken for carcinoma of the prostate in two patients Nodular hyperplasia, upon rectal examination, may present the same clinical appearance as carcinoma, but the nodules in such cases are not stony hard

TREATMENT

Palliative Palliative treatment has been used in patients who showed metastases or evidence of local extension beyond the limits of surgical excision In the series of 136 patients, this has been the only possible treatment in 62 (45 5 per cent)

Palliative treatment consists of estrogen therapy, castration, transurethral resection, suprapubic cystostomy, roentgen therapy, and prefrontal lobotomy and

TABLE 4. *Carcinoma of the prostate; follow-up*

YEAR	PATIENTS, TOTAL FOR YEAR		LIVING		DEAD		UNKNOWN	
	Palliative	Radical	Palliative	Radical	Palliative	Radical	Palliative	Radical
1940	9	1			8	1	1	
1931	3	0			3			
1942	4	0			4			
1943	3	1	2		1	1		
1944	2	2	2	1		1		
1945	0	2		1				1
1946	4	3	1	2	3			1
1947	5	13		7	5	4		2
1948	5	9	1	3	4	3		3
1949	4	8		6	4			2
1950	6	14		13	5	1	1	
1951	8	12	4	11	1		3	1
1952	9	9	8	9	1			

TABLE 5. *Carcinoma of prostate; over 5 year survival (1940–1952)*

TOTAL PTS FOR PERIOD		LIVING		DEAD		UNKNOWN	
Palliative	Radical	Palliative	Radical	Palliative	Radical	Palliative	Radical
30	22	8	11	20	7	2	4
Percentage............		26%	50%	67%	31%	6%	18%

adrenalectomy. Estrogen therapy and castration are instituted as soon as radical excision is considered impracticable. Transurethral resection has been used for urinary obstruction in 19 patients, prefrontal lobotomy in three, and cystostomy drainage in two. Adrenalectomy has been performed in three patients for relief of pain after other palliative measures have failed.

Curative. Complete surgical excision of the involved structures is the only procedure which will effect a cure. Radical perineal prostatectomy—removal of the prostate, capsule and seminal vesicles—has been done in 74 patients (54.5 per cent, table 3). This high percentage of radical procedures has been attained because of the requirements of the annual physical examination of military personnel, which includes a digital rectal examination.

Gold isotope therapy, according to the Flocks technique,[4] has been investigated but not evaluated. Preoperative estrogen therapy has been used[5] and may have extended the indication for radical surgery.

The tissue removed by radical excision is thoroughly evaluated. If the microscopic study indicates that the entire malignant area has been removed, no further treatment is given. In case the tissues beyond the capsule are involved, castration and estrogen therapy are instituted without delay. Postoperative follow-up, x-rays, and acid phosphatase determination are done at 3 month intervals during the first year, at 6 month intervals the second year, and annually thereafter

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PROGNOSIS

Tables 4 and 5 indicate the number of patients subjected to conservative and radical procedures by year, and their status to date Following is an analysis of patients observed for five years or longer

The increased survival rate of patients subjected to radical perineal prostatectomy over those subjected to conservative procedure is evident The survival rate for those in the conservative group is 26 per cent, and for the radical group, the 5 year survival rate is 50 per cent

In the conservative group, the majority of the patients who died, died of carcinoma of the prostate Of the seven dead in the radical treatment group, 4 died of carcinoma of the prostate at 2, 23, 26, and 30 months, respectively The other three died of other causes, one at 16 months of postoperative bronchogenic cancer, one at 31 months of a coronary occlusion, and one of a cerebral vascular accident at 49 months

CONCLUSIONS

The high percentage of patients found suitable for radical perineal prostatectomy is attributed to the required digital rectal examination which is a part of the Army's routine annual physical examination in men over 40 Complete surgican excision of the involved tissue following early diagnosis is the only procedure which will effect a cure in cancer of the prostate

All males over 40 years of age should have an annual digital rectal examination to detect early evidence of cancer of the prostate Suspicious glands should be examined more frequently for evidence of change

In the event evidence is found indicating that the malignant process has not been completely extirpated, orchiectomy and estrogen therapy should be instituted without delay

SUMMARY

Results of cancer of the prostate have been presented

Five year survival and death rates of those subjected to conservative and radical measures have been presented

Complete excision of involved tissue is advocated as soon as diagnosis is established

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A TRUE HERMAPHRODITE

WILLARD E. GOODWIN,* PETER L. SCARDINO,† AND WILLIAM WALLACE SCOTT

From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital, Baltimore, Md.

Proven cases of true hermaphroditism are still sufficiently rare to be reported. Capon (1951) has recently described the forty-first example of this unusual developmental abnormality.

E. C. (J. H. H. No. 448,002) was born of a normal, healthy Negro mother, on December 16, 1933. "He" was her first child. There were no known developmental abnormalities in the family. The intern's physical examination after delivery described an otherwise normal, healthy, 2925 gm. male baby with a congenital anomaly of the external genitalia presumed to represent hypospadias, chordee and male pseudohermaphroditism with an undescended left testis. The child was reared as a boy.

He was frequently seen in the pediatric and other dispensaries of the hospital for minor illnesses and routine observation. An apparently normal male childhood was complicated only by primary pulmonary tuberculosis which healed after a year of rest in 1943. There are notes in the chart by many observers concerning the genital anomaly which was scheduled for surgical correction after puberty. The possibility of true intersexuality was never considered at that time.

On September 3, 1948, he entered the hospital by way of the Accident Room with the complaint of severe lower abdominal pain. No definite diagnosis was established, but it seemed in retrospect that the pain may have represented "mittelschmerz" or menstrual cramps. He was admitted to the urological service the next day.

Examination revealed a well-developed 14-year-old Negro who appeared to be more female than male (fig. 1). There was a feminine distribution of pubic hair and body fat. The breasts were about normal for a 14-year-old girl, and there was a small vaginal opening. The phallus was small for a 14-year-old boy and showed a marked chordee. Nonetheless it looked more like a penis than a clitoris. There was a small testis in normal position in the right side of the bifid scrotum; on the left side there was only an empty scrotal or labial pouch (fig. 2). There were no hernias. Vaginal examination could not be done, but rectal examination gave the impression that there was a small uterus lying to the left of the midline in normal position. No prostate was felt. The urethral meatus opened about 2 cm. inside the vagina on the anterior vaginal wall. The patient was otherwise normal.

Laboratory studies were within normal limits. Preoperative urinary 17-ketosteroids were 6 mg./day, and urinary follicle-stimulating hormone was estimated at 13 m. u./day. Estrogens were not determined before operation.

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* W. E. G.: Deptarment of Surgery, Division of Urology, School of Medicine; The University of California at Los Angeles.

† P. L. S.: 2515 Habersham St., Savannah, Ga.

Presented to the Los Angeles Urological Society, March 3, 1953.

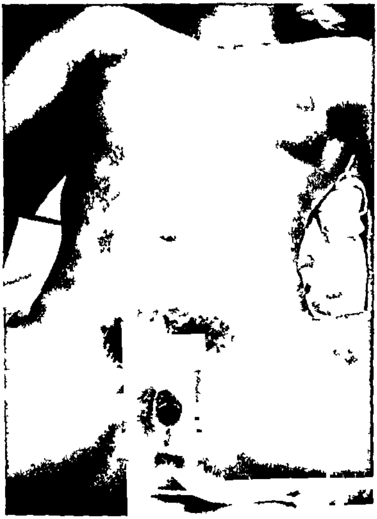

Fig 1

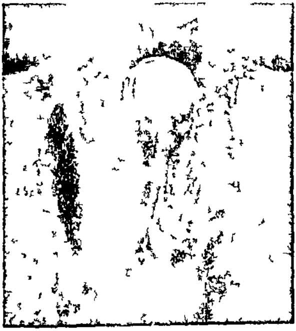

Fig 2

Fig 1 Well developed 14 year old Negro who appeared to be more female than male

Fig 2 Note penis with chordee bifid scrotum right scrotum testis, absence of left scrotal gonad vagina (orifice marked by white fluid escaping after vaginogram in figure 3) Urethral meatus opened about 2 cm inside vaginal canal

Under ether anesthesia, cystoscopy, vaginal examination, and a combined vaginogram and cystogram were made The note states, "There is a chordee of the rather well developed phallus There is a small vaginal orifice, and no urethra is seen externally The mucosa of the vagina extends outward where the urethra should be almost to the tip of the glans The labia are large and well developed The labium on the right side contains a small and easily palpable gonad which feels like an underdeveloped testis There is a palpable epididymis There is no external gonad on the left Combined abdominal rectal examination with the patient well relaxed confirms the previous examination, indicating a uterus and ovary on the left side of the pelvis Cystoscopy, done through the female like urethra 2 cm inside the vaginal opening, reveals a normal bladder, trigone, and ureteral orifices The vesical neck appears more female than male, and no definite prostatic urethra is identified " The combined vaginogram (with Rayopaque) and cystogram (with 20 per cent Skiodan) revealed a normal bladder and a small vagina and cervical canal extending upward and to the left behind the bladder (fig 3) Another x ray of the pelvis to determine bony characteristics was interpreted as showing normal male configuration

The decision as to treatment, if any, was interesting Physically the patient appeared to be more female than male, and it would have been surgically more simple to conform with this apparent inclination of nature However, he had

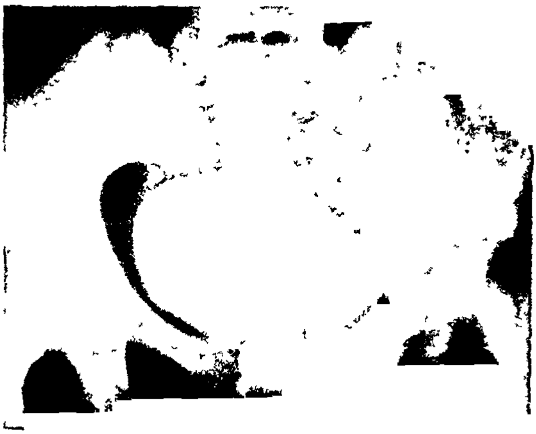

FIG. 3. Combined cystogram and vaginogram

been reared as a male and was psychologically oriented toward "maleness" as was his mother who wanted a boy. The possibility of making the patient a female seemed out of the question here.

A psychiatric interview reported by Dr. James D. Carter was interesting: "An interest was expressed by the urologist in the attitudes of the patient with regard to himself and others of both sexes. The patient answered questions readily and frankly asked questions. He did not appear to be particularly embarrassed, worried, anxious, or depressed. In fact, I was rather amazed at how well he seemed, at least superficially, to adjust to his predicament.

"*Mental status examination.* The patient had the appearance of an attractive young colored girl. The facial features were soft and round and the skin very smooth. However, the patient certainly would not look peculiar if he were dressed in men's clothing. He might simply look a little effeminate. There was nothing effeminate in the patient's gestures or expressions. Talk: Normal masculine adolescent. Voice a little high-pitched and soft, but could certainly be accepted as a masculine voice. Orientation, concentration, thought content, general information, and judgment were all normal.

"The mother's story corroborates the patient's in detail. She states that he seems to be a normal boy. He has never given her any trouble and always seemed to her to be happy and well adjusted.

"*Impression.* I was amazed at how well this patient has adjusted to this difficulty. I found no evidence of neurotic or psychotic mechanisms. The patient's compensations are obvious; for example, his boastfulness about his courage and strength. These compensations seem to serve him well.

"*Recommendations.* 1) From a psychiatric standpoint, it would seem extremely difficult for this patient to change his sex and so the patient should remain a male. 2) The patient, I believe, will feel much more comfortable following the surgical procedures which are planned for him: removal of breasts and correction of hypospadias. 3) The patient is anxious and willing to talk to one of the urologists regarding his condition. I don't see any necessity for going into technical detail, but the patient's condition should be described superficially to him if he

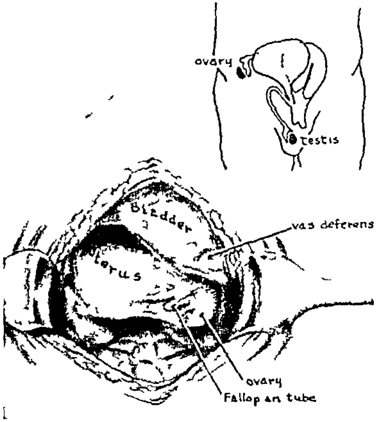

FIG. 4. View of pelvis from above (symphysis at top of drawing) Uterus lay to left, and curiously ovary and tube were on right side of uterus, same side as testis and vas Insert shows diagrammatic representation of relationships of ovary, tube and uterus and of testis and vas as viewed from in front

asks about it There would be no point in telling him that he had an ovary, tube, and uterus, but he should be told that he will never have children and that anatomically he will never be exactly like other males He will be greatly encouraged by the comment that following the operation he will be much more male than he has been in the past "

Because of the patient's desire to be "like the other boys" it was determined to remove all female elements and attempt the usual reconstruction of the male external genitalia

On September 10, 1948, the following operation was performed exploratory laparotomy, panhysterectomy, left oophorectomy and salpingectomy, appendectomy and biopsy of right testis, vas, seminal vesicle, prostate, and breast

A low midline incision opened the peritoneal cavity A small uterus, fallopian tube and ovary lay on the left side of the pelvis (fig 4) The ovary and tube, however, lay to the right of the uterus, a curious finding as the testis was also on the right side in the scrotum Total hysterectomy, together with removal of a small flap of vagina, was done The adrenal glands were palpated transperitoneally and seemed to be normal Then the right scrotal testis and epididymis were biopsied A small mass (prostate) at the base of the bladder was biopsied together with a portion of the vas (fig 5)

The pathologist's note described normal microscopic specimens of ovary, uterus, fallopian tube, testis (without spermatogenesis), seminal vesicle, epididymis, vas deferens, and breast (predominantly male) (figs 6, 7, 8, 9, 10) The prostate showed marked squamous metaplasia of acinar epithelium, a striking example of estrogen effect on the prostate (fig 8, *B*)

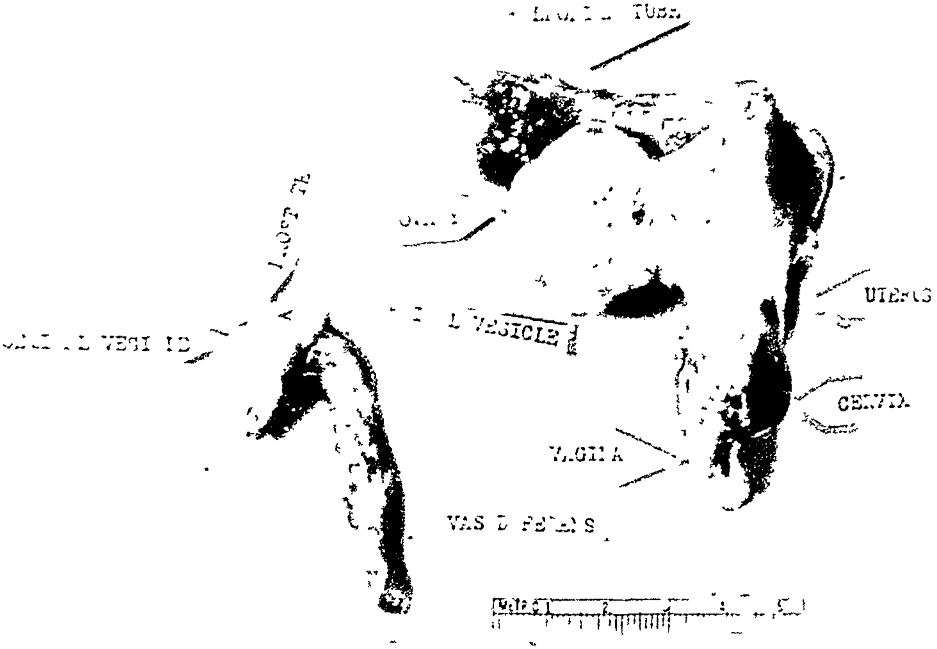

Fig 5. Gross appearance of operative specimens

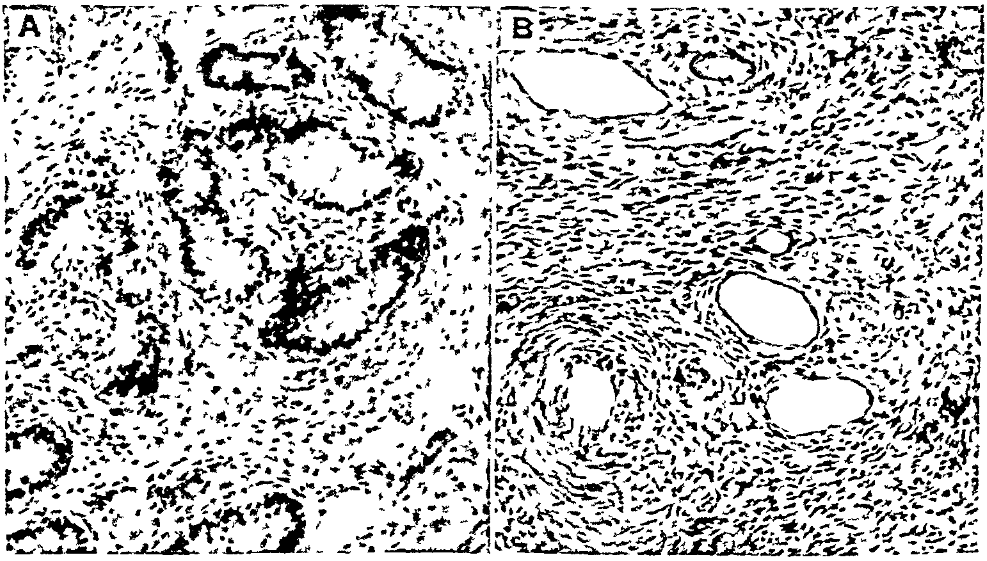

Fig. 6. *A*, testis (aspermatogenesis). *B*, ovary. × 150

Fifteen days after the first operation, plastic repair of the chordee and closure of the vagina were done. Cystostomy was done to divert the urinary stream. The penis was straightened in the usual manner. Vaginectomy was done from below, and the anterior wall of the vagina was used to extend the urethra outward to the perineum (fig. 11).

At a later admission an attempt was made to construct a urethra to the end of the penis using a split thickness free graft of skin from the thigh. This failed

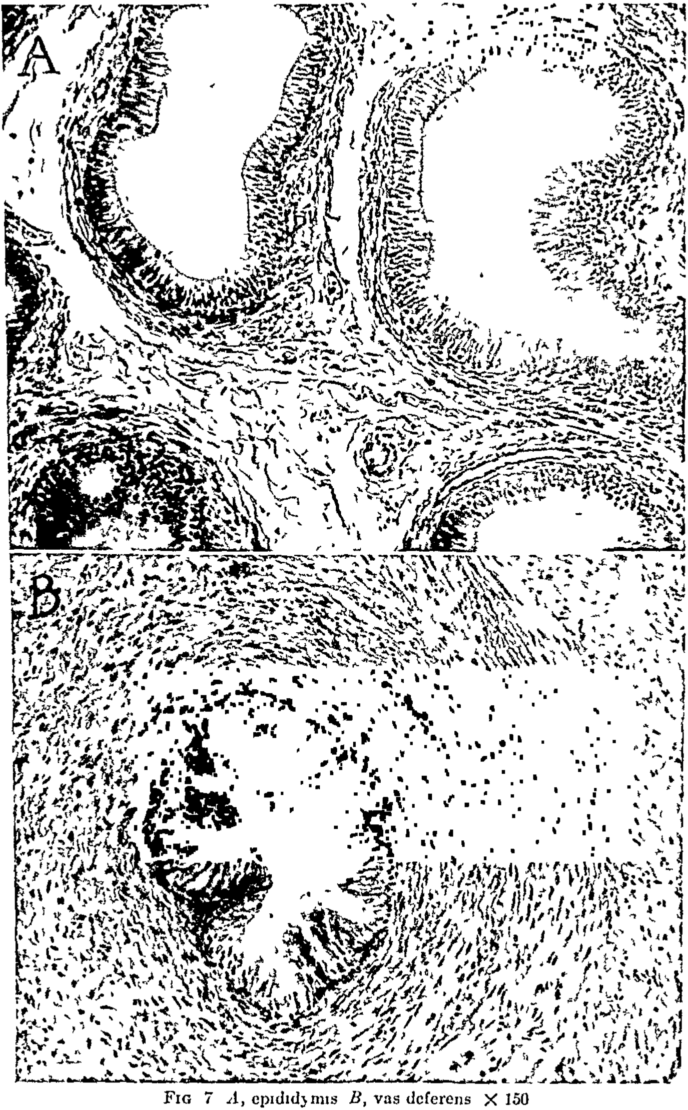

FIG 7 *A*, epididymis *B*, vas deferens × 150

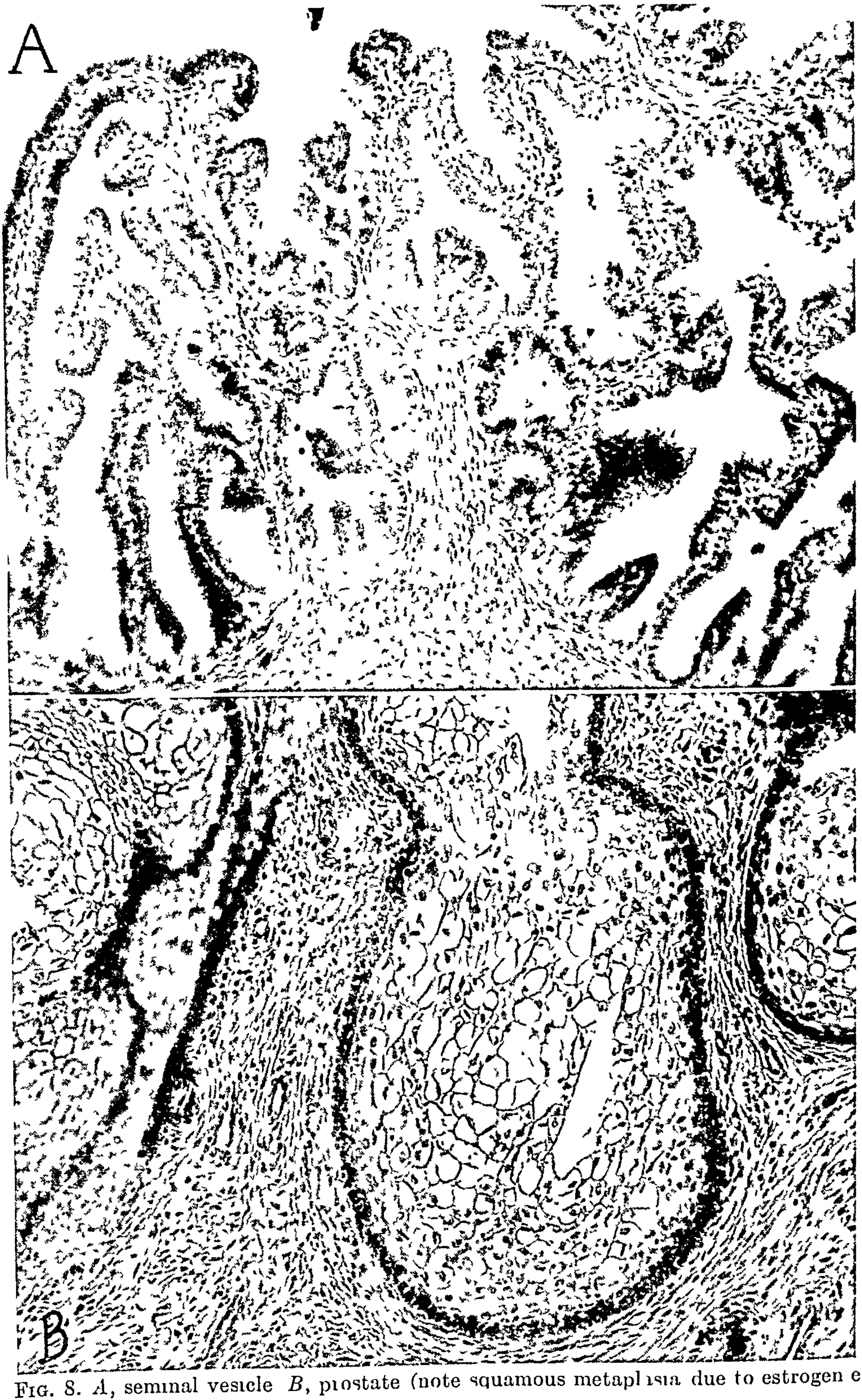

FIG. 8. *A*, seminal vesicle *B*, prostate (note squamous metaplasia due to estrogen effect × 150

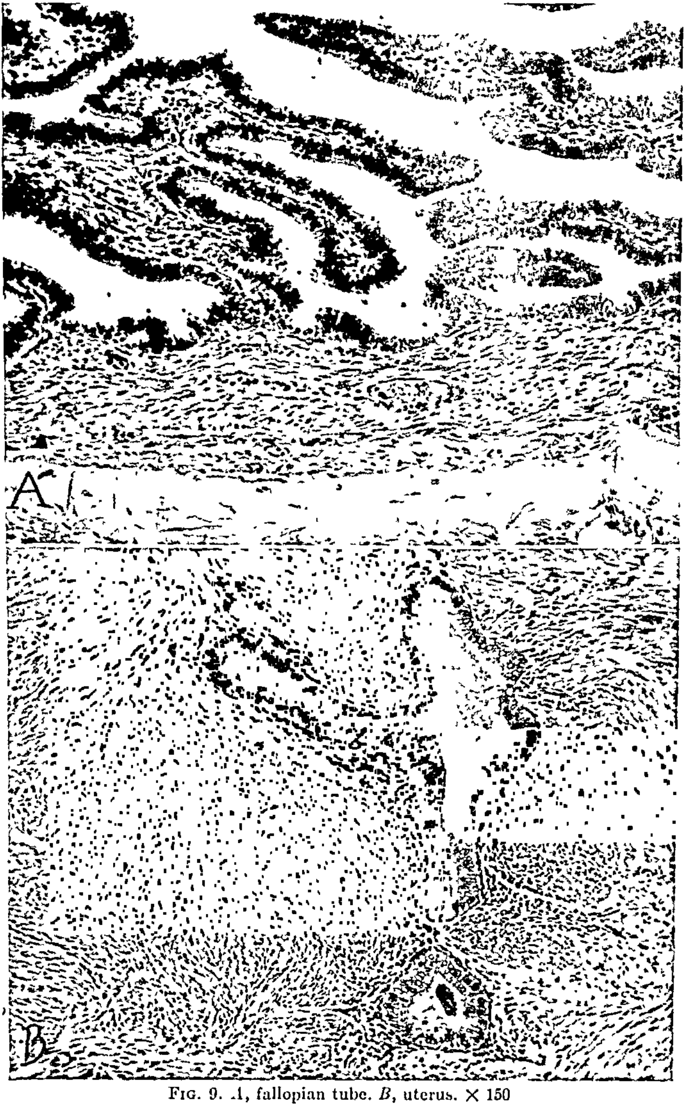

FIG. 9. *A*, fallopian tube. *B*, uterus. × 150

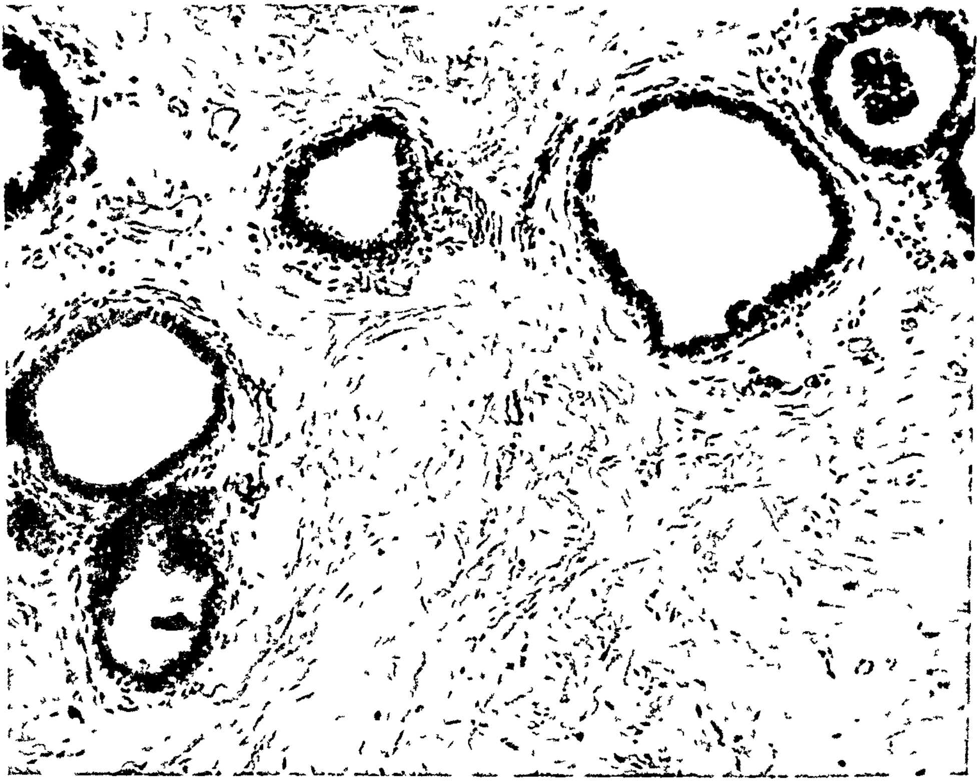

FIG 10 Breast × 150

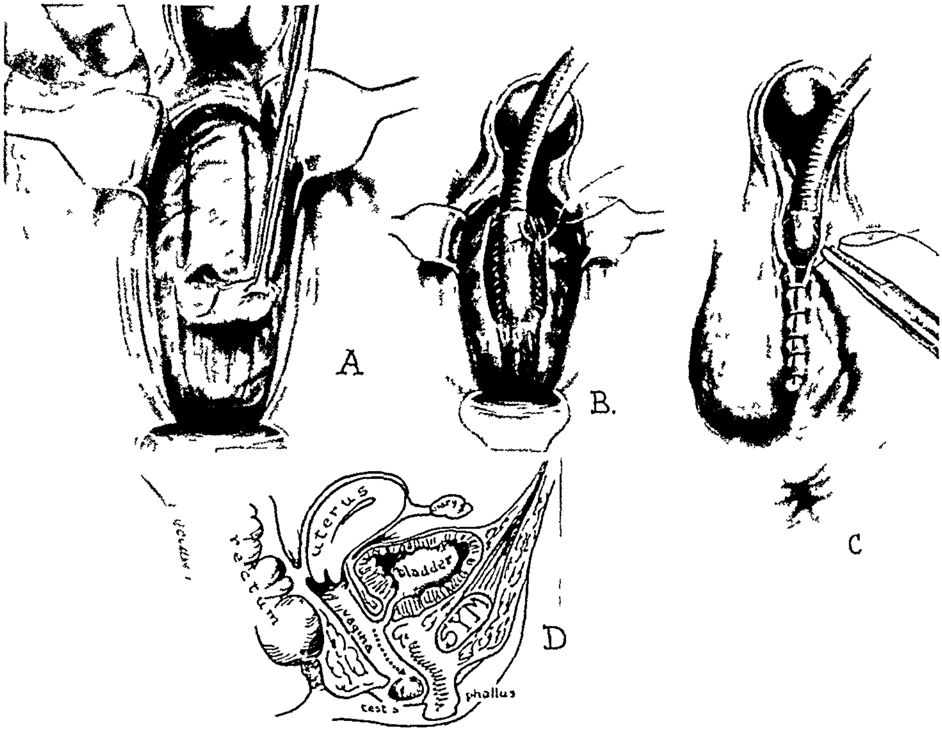

FIG 11 Method of vaginectomy using anterior vaginal wall to extend urethra so that new meatus lies well forward on perineum Inset shows preoperative relationships in sagittal section

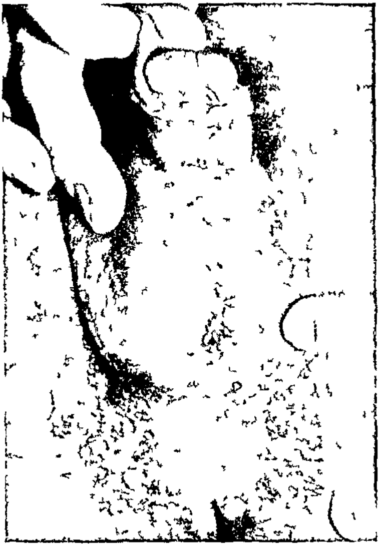

FIG 12 Perineal urethrostomy from which patient is able to void standing

because of scar formation, and the patient was left with a perineal urethrostomy from which he easily voids standing (fig 12) He refused further treatment but has been seen at regular follow up visits since then

Three months after the first operation, urinary 17 ketosteroids were 5 93 mg /day, and FSH assay was ‘slightly positive," 52 m u /24 hours An estrogen assay showed 7 5 gamma per 24 hours

He was seen on May 22, 1951 (2 years and 8 months postoperatively) At that time it was noted, "He is now 17 years old and works as a bus boy He appears more mature in speech and action but his physical appearance has changed very little He has grown little or none in height though his weight has increased due to fattening around the waist His breasts are still enlarged and about the same size though he thinks they may be smaller (He had to be excused from gym class in school because of this) He has no complaints except fear that he may be drafted into the Army He says that his appetite is normal and that he feels well and gets along well in his job He says that he has fairly frequent erections either spontaneously or when playing with his girl friends He says that the penis is straight He states he has not attempted intercourse and indicates that he is not greatly interested in it He says that during sexual arousal the nipples of his breasts become slightly erect This is also true when he is cold He denies nocturnal emissions and masturbation He is indefinite about whether or not he has ever had a sensation of ejaculation or orgasm All scars are well healed and soft The penis is straight There is abundant prepuce and an excess of "scrotal" skin The left scrotum is empty On the right there is a mass approximately 3 by 2 cm. which seems to be testis. Distal to this is a worm-like structure which is smaller and softer and which is probably epididymis. It does not seem directly attached to the testis. He voids a good stream while standing with the urine coming from the perineal urethrostomy. Rectal examinations reveal no normal prostate. There is, however, a small structure approximately 2 by 1½ cm. which has the consistency of prostatic tissue and is in the position of the prostate. No rectal or abdominal masses are felt."

Plastic mastectomy and further urethral construction were offered to him, but he refused for the time being.

He was most recently seen in February 1952 by Dr. Paul Bunce who reported, "The patient returned with a severe urinary tract infection. He was having frequency, nocturia, and some burning; and a complete study showed that it was apparently on the basis of cystitis. Pyelograms were normal, and cystoscopy through his perineal meatus showed acute cystitis. There were a few hairs in the urethra. I think the cause of his troubles must have been just the female type of cystitis, probably precipitated by the hairs growing in the urethra. He responded well to Gantrisin, and the plan is to give him depilatory doses of x-ray. He is working in a laundry and is the prime support for his family."

SUMMARY

A proven case of true hermaphroditism is recorded.

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RELATIVE INCIDENCE OF PEDIATRIC UROLOGICAL CONDITIONS

JOHN K LATTIMER AND MIRIAM HUBBARD, R N

From the Squier Urological Clinic and The Babies Hospital Columbia Presbyterian Medical Center, New York, N Y

How frequently can the practicing urologist expect to see the various pediatric urological conditions which are described in the literature? In an effort to answer this question a study has been made of the last 2,063 consecutive new admissions to the pediatric urological service at the Columbia University Medical Center in New York City Of these patients, 45 per cent were hospitalized because of a congenital anomaly, 11 per cent because of uncomplicated infection and 2 per cent because of tumors The remaining 42 per cent made up a large miscellaneous group who came in for circumcision, enuresis, frequency, abdominal pain, injury, etc (table 1)

This survey covered an 11½ year period from November 1, 1941 to March 30, 1953 It did not include re admissions, as for multiple stage operations or for follow-up Neither did it include patients who were treated only in the out-patient department but not admitted to hospital beds There were 44,274 admissions to the entire Babies Hospital during this same 11½ year period, but this total of 44,274 represented an unknown number of re admissions The total number of admissions to the pediatric urological service during the same period was 3,024 This figure included approximately 1,000 re admissions All of the patients were under 13 years of age Each patient was listed under only one diagnosis Many of the patients who had congenital anomalies or strictures also had infections They were listed only under the heading of anomaly or stricture, however, since the infection was considered to be merely a complication of the more basic diagnosis If multiple anomalies were present, such as exstrophy and epispadias, the patient was listed under the more major diagnosis, namely exstrophy of the bladder

The patients were first listed in order of the frequency of the various diagnoses (table 2) It was realized that some diseases were seen more frequently than usual at this hospital because of the interest of some staff members in particular problems For instance, Dr Cahill's particular interest in diseases of the adrenal gland has probably brought more cases of adrenal disease to this hospital than would normally be expected Increased interest in tuberculosis of the kidneys at this hospital has not yet caused a greater influx of patients with tuberculosis of the kidney, at least to the pediatric service The 16 cases with kidney tuberculosis were culled from the normal flow of clinic patients as they were seen in the out-patient department Interest in the detection of this disease has perhaps been heightened here by recent developments in the chemotherapy of tuberculosis, however

Read at annual meeting, American Urological Association, St Louis, Mo May 13, 1954

TABLE 1. *2000 pediatric urological patients*

	PER CENT
Anomalies	45
Infections	11
Tumors	2
Misc: (Phimosis, enuresis, stricture, injury, no g.u. disease, etc.	42

DISORDERS OF THE KIDNEY, KIDNEY PELVIS AND URETER

Multiple kidney pelvis was diagnosed in 50 cases (2½ per cent). It was notable that 80 per cent of the patients with this condition were females. There were 11 patients with double ureter, where one ureter had an ectopic orifice in the vagina or posterior urethra. Eight patients had double ureter, the upper one of which ended in a ureterocele. Both of these categories were treated by heminephrectomy and ureterectomy. There was one patient with a triple ureter on one side (table 3).

Hydronephrosis was the principal diagnosis in 138 cases (7 per cent). This disorder was associated with many different causes. In one large group of patients the hydronephrosis was due to a generalized flaccid dilatation of the ureters, bladder and pelvis, probably on a "neuromuscular" basis. Most of the surgical procedures ever suggested for this condition have been tried here and have led to the conclusion that ureteral surgery is not the best treatment for most of these patients. Research is now under way into the mechanism and treatment of this condition, with the help of an interested neurosurgeon. Experimental hydronephroses, hydro-ureters and dilated bladders have been created in cats. The nerve pathways leading to the bladder and ureters and to the sphincters have then had electrodes planted in them which lead to an induction coil buried under the cat's skin. When these electrodes are stimulated by external impulses, the cat can be made to urinate or ejaculate as desired. It is hoped that these studies will contribute information eventually leading to improved therapeutic techniques. A cystogram of one of these cats shows the coil in place and shows the bladder before and after stimulation. The large neurogenic type bladder has been emptied except for a small amount of residual urine. We are now trying to get rid of this residual urine. We are also endeavoring to reproduce experimentally the various types of neuromuscular and neurological disorders of the bladder which are seen in pediatric patients.

Many additional cases of hydronephrosis were unlisted under this diagnosis because they were present in the cases included under horseshoe kidney, pyelonephritis, deficiency of abdominal musculature and exstrophy of bladder.

Pyelonephritis was the major diagnosis in 120 cases (5.8 per cent) of the patients. The degree of severity was not considered for this study. All of these particular cases had nonspecific infections with pyogenic organisms. There were 16 additional cases of tuberculosis of the kidney, however. Many additional unlisted cases of pyelonephritis were seen as complications of obstructive lesions.

Cystic degeneration of the kidney was diagnosed more often (9 cases) than polycystic disease (4 cases), as might be expected in this young age group. Hypoplastic kidney was encountered five times, malrotation three times, ab-

TABLE 2 *2063 pediatric urological admission diagnoses listed in order of the frequency of their occurrence (no readmissions included)*

ORDER OF FREQUENCY		NUMBER OF CASES		PER CENT
1	Phimosis or redundant prepuce		393	19.1
2	Undescended testis			
	Unilateral	193		
	Bilateral	49		
		242	242	11.8
3	Enuresis and frequency		173	8.4
4	No urological disease found		142	6.9
5	Hydronephrosis		138	6.7
6	Hydrocele		124	6.0
7	Pyelonephritis (nontuberculous)		120	5.8
8	Stricture of urethra (including meatus)		114	5.5
9	Hypospadias		104	5.0
10	Congenital deformity of kidney (table 3)		82	4.0
11	Adrenal and genital abnormalities			
	Adrenogenitalism and pseudohermaphroditism	36		
	Precocious puberty	3		
	Hypergenitalism	3		
	Fröhlich's	4		
	True hermaphroditism	2		
	Hypogenitalism	3		
	Masculinizing adrenal adenoma	4		
	Masculinizing adrenal carcinoma	2		
	Pheochromocytoma	3		
	Sympathicoblastoma	4		
	Hirsutism	1		
	Gynecomastia	1		
	Interstitial cell tumor of testis	1		
	Ovarian cyst	2		
	Double penis	1		
	Double vagina	2		
	Absent testis	2		
		74	74	3.5
12	Neurogenic bladder		56	2.7
13	Cystitis		49	2.3
14	Injuries to genito urinary organs (table 4)		34	1.6
15	Hernia		33	1.6
16	Wilms tumor		27	1.3
17	Exstrophy of bladder		26	1.3
18	Miscellaneous infections, cysts, etc. of penis, testes and prostate		18	0.9
19	Fistula			
	Urethrorectal	10		
	Rectovaginal	1		
	Imperforate septa of anus	5		
	Imperforate vagina	1		
		17	17	0.8

TABLE 2.—(*Continued*)

ORDER OF FREQUENCY		NUMBER OF CASES	PER CENT
20	Deficient abdominal musculature with hydronephrosis and cryptorchidism	16	0.8
21	Tuberculosis of kidney	16	0.8
22.	Renal calculi	12	0.6
23	Diverticulum of bladder	12	0.6
24	Vaginitis and urethritis	10	0.5
25	Epispadias	7	0.4
26	Patent urachus	7	0.4
27	Sulfa drug reactions involving the kidney	5	0.2
28	Hemophilia with hematuria	5	0.2
29	Epididymitis	2	
30	Renal calcinosis	2	
31	Pelvic abscess	2	
32	Bladder papilloma	1	0.3
Total		2063	100

TABLE 3 *Congenital deformity of kidney, 4 per cent*

Double pelvis	30
Double ureter, 1 orifice ectopic	11
Double ureter, with ureterocele	8
Triple ureter	1
Horseshoe kidney	9
Cystic degen. of kidney	9
Polycystic kidney	4
Hypoplastic kidney	5
Malrotation of kidney	3
Absent kidney	2
Ectopic kidney	1

TABLE 4 *Injuries, 1 per cent*
(*among 2000 pediatric genito-urinary patients*)

Kidney rupture	11
Penis (circumcisional, fract. pelvis)	6
Perineum	3
Scrotum	2
Testis	1
Torsion testis	5
Torsion hydatid	1
Foreign body bladder	5

sent kidney twice and ectopic kidney only once. Five patients, early in the series, had reactions to sulfa drugs; two with moderate oliguria, one with hematuria and two with anuria. Hematuria due to hemophilia was encountered in five patients. A congenital deficiency of the abdominal musculature, accompanied by hydronephrosis, undescended testes and other anomalies was encountered in sixteen

TABLE 5 *Tumors, 2 per cent*
(among 2000 pediatric genito urinary patients)

Wilms	27
Sympathicoblastoma	4
Masculinizing adrenal adenoma	4
Pheochromocytoma	3
Ca adrenal	2
Ovarian cyst	2
Interstitial cell tumor of testis	1
Papilloma bladder	1
Total cases	44

instances among this sample of 2,063 patients Injuries to the kidneys occurred 11 times (table 4)

ADRENAL AND GENITAL ABNORMALITIES

Adrenogenitalism (pseudohermaphroditism or virilism) was found in 36 patients, presumably due to hypertrophy or faulty secretion by the adrenal cortex *These patients are now being treated by cortisone Precocious puberty* was found in 3 patients, hypergenitalism in 3, true hermaphroditism in 2, hypogenitalism in 3, masculinizing benign adrenal adenoma in 4 cases (wherein the patient suddenly became *virile after being normal up until that point) There* were also 2 cases of carcinoma of the adrenal and 3 cases with pheochromocytoma, as well as 4 with sympathicoblastoma There was 1 interstitial cell tumor of the testis (table 5)

Undescended testis was the primary diagnosis in 242 patients, 49 of whom (20 per cent of the 242) were bilateral The remaining 193 were unilateral This group constituted approximately 12 per cent of our total sample of 2,062 patients and pointed up the necessity for all urologists in-training to develop a good technique for orchiopexy This is a condition which they will obviously be seeing in their urological practice Hyposadias was the diagnosis in 104 (5 per cent) of *the patients* Many methods of repair have been investigated on this service and the Cecil type of procedure is currently our first choice A few additional unlisted cases of hypospadias were found, of course, among those children with a diagnosis of pseudo or *true hermaphroditism* Additional or unlisted cases of undescended testis were present among the pseudo and true hermaphrodites and among the patients with congenital deficiency of the abdominal musculature Exstrophy of the bladder occurred in 26 patients *among these 2,063* Seven patients had epispadias Enuresis and frequency were the only diagnoses among 173 patients (8 4 per cent) Additional patients had enuresis, however, who were circumcized and therefore included under the listing of redundant prepuce or *phimosis* There were 114 patients (5 5 per cent) with stricture of the urethra, mostly of the meatus Five more had strictures resulting *from* injury In 3 of these cases, injury was due to accidents during circumcision elsewhere, at which time the glans penis was *inadvertently* removed and a stricture of the urethral stump resulted Only 7 of the 51 cases of urethral structures were located at the bladder neck, and in only 3 of these 2,063 cases were well defined valves (membranes) found across the urethra just distal to the verumontanum. Two of these 3 patients died within a few days after birth. It has been our experience that this condition occurs very rarely and that very few of these patients survive beyond the first few days, because of the destruction of the kidneys due to back pressure from the urine secreted during intra-uterine life. True valves of the urethra are apparently rare, at least in our experience, in spite of the frequent reference to them in the literature. We have had one additional case where the passage of a sound during the first weeks of life resulted in the patient's being able to void fairly well subsequently. This patient was explored retropubically at the age of 2 years and no definite valves could be found although there were low ridges within the external sphincter. These were incised when the urethra was opened via the retropubic route. Following this maneuver several diverticula of the bladder, which were pressing on one ureter and causing hydro-ureter, were also excised.

INJURIES AND CALCULI

A summary of the injuries to the genito-urinary tract is found in table 4. The low number of injuries may be due to the fact that this hospital does not maintain an ambulance service. Only 12 cases of urinary calculi were found among the 2,063 patients examined. This low incidence probably reflects the temperate, humid climate of New York City.

SUMMARY

A sampling from the experience of one pediatric urological service has been presented. Two thousand and sixty-three individual admission diagnoses were catalogued. The largest and most significant single group was made up of patients with congenital anomalies (45 per cent), the second largest group was made up of those with infections (11 per cent). Only a small percentage (2 per cent) of the patients were admitted because of tumors of the genito-urinary tract or adrenal glands. Overlapping of the various groups was frequent. Additional and more comprehensive analyses of the pediatric urological admissions to this service will be reported periodically.

Acknowledgement is made here of the courtesy of Drs. Cahill, Fish, Robinson, Hazzard, Melicow, Yeaw, Sullivan and Seidel in permitting the inclusion of some of their patients in these series.

180 Fort Washington Ave., New York 32, N. Y.

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CLINICALLY INNOCUOUS EFFECT OF INTRAVENOUSLY ADMINISTERED DISTILLED WATER

IRVING VICTOR

The adverse effects of intravascular hemoslyis have been widely described (Creevy,[1] Nesbit et al,[2] and Flink[3]) Many urologists have employed isotonic irrigating solutions for transurethral surgery in order to prevent the allegedly deleterious effects of laking red blood cells within the extracellular compartment

Recently I have observed two patients who inadvertently received distilled water intravenously without serious effects It is the purpose of this clinical note to offer these unexplained data in the hope that further study will be made

R H, a 31 year old divorced Negress, was admitted to the Georgia Infirmary, Savannah, Georgia acutely ill Temperature 102F, nonprotein nitrogen 145 mg per cent She had positive sickling of the red cells The patient had nausea and vomiting and complained of vague lower abdominal distress Urine on admission was grossly bloody Cystoscopy revealed bloody spurts from both ureteral orifices The patient was treated expectantly with whole blood and parenteral fluid with fair response She was inadvertently given a total of six liters of distilled water in equally divided amounts for six consecutive nights To our great surprise the hematuria abruptly terminated during the administration of the fluid and the nonprotein nitrogen value returned to normal over a six day period At no time was urinary output diminished

Mrs J E H, a 32 year old white married woman, was admitted to the Warren A Candler Hospital, Savannah, Georgia for exploratory laporotomy and was found to have a right tubo ovarian abscess at surgery After removal of the surgical specimen, it was discovered that the distal 10 cm of the right ureter had been removed Urological consultation resulted in ureteroneocystostomy Two liters of distilled water were inadvertently administered intravenously during the first postoperative day without harmful effects, save hemoglobinuria Urinary output did not diminish The patient was discharged on the eighteenth postoperative day, improved

DISCUSSION

Intravascular hemolysis produces no ill-effects *per se*, according to the reports of Creevy,[1] Hamilton et al,[4] and Yuile [5] Whether the erythrocytic stroma released by laking and the lipo and muco proteins therein contained exercise an unfavorable effect is speculative (A L Finkle[6]) It is unlikely that "blood phenols,"

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[1] Creevy, C D J Urol, 58 125-131, 1947

[2] Nesbit R M and Glickman, S I J Urol 59 1212 1216, 1948

[3] Flink E B Blood transfusion studies III The relationship of hemoglo
of the pH of the u
dogs J Lab and

[4] Hamilton, P
in dogs in hemorr [illegible]

[5] Yuile C L Hemoglobinuria Physiol Rev, 22 19 31, 1942

[6] Finkle, A L Personal communication

said to be elevated in uremia, were flushed away by the intravenously administered water, thus accounting for the favorable clinical effect in the first patient. It is also unlikely that sickling of the erythrocytes would interfere with the release of hemoglobin, since these cells are no more fragile than normal ones. Since the cause of uremia is unknown (Snapper and Schaeffer[7]) ameliorative results in uremic patients cannot be accurately identified.

COMMENT

Two cases of intravascular hemolysis caused by the inadvertent intravenous infusion of distilled water are presented.

The first patient suffered uremia and hematuria associated with sicklemia; both former conditions appeared improved after the administration of the hypotonic solution. This, of course, may have been happenstance, but, it certainly merits further consideration. Case 2, postoperative salpingo-oophrectomy complicated by surgical trauma to the ureter, suffered no adverse effects secondary to having received distilled water by vein.

It is not the purpose of this brief note to suggest any hypotheses as to the mechanism producing the results noted clinically. It is hoped that further study will be undertaken to elucidate this very fascinating problem.

228 E. Huntingdon St., Savannah, Ga.

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[7] Snapper, I. and Schaefer, L. E.: Treatment of two patients with hepatorenal syndrome and acute renal failure by exsanguinotransfusion. Ann. Int. Med., **34**: 692–704, 1951.

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A NEW CATHETER FOR PEDIATRIC USE

S P R HUTCHINS

From Department of Urology, Baylor University College of Medicine, Houston, Texas

In catheterizing and dilating infants and children, it was believed that a safer and still more practical instrument than those available was needed Catheterizations are not always easy, and it is not without risk to pass sounds and dilate the urethra of a combative child even though plenty of help is available for restraint Obviously one cannot give an anesthetic each time a dilatation is needed

It had been noted in dilating small caliber strictures in men that filiforms and Phillips catheters caused less pain and seemed less traumatic than Le Fort sounds of like caliber The only drawback to the use of filiforms and Phillips catheters was the rigid straight section necessitated by the metal parts The straight section deforms the natural curve of the urethra as it passes Phillips whip catheters, having no straight rigid section, were next used and found to be the least traumatic and the most satisfactory

Recalling the above, Phillips whip catheters were used on some uncooperative children of both sexes These worked better but were too long and unwieldy and contamination occurred easily A shortened whip catheter was then designed and turned over to a manufacturer (C R Bard, Inc) for production The total length is approximately one-half that of the Phillips whip catheter The range is from 8 to 18F in even sizes

These flexible catheters can be used as sounds by holding the finger over the open end of the catheter as the urethra is dilated until the desired maximum size is reached, then a specimen can be obtained and the bladder emptied If the bladder has been emptied for a specimen by the first catheter passed, sterile water can be used to partially fill the bladder The author prefers to dilate the urethra of a resisting pediatric patient only when the bladder is partially filled, thus giving space for the filiform portion of the catheter to curl in and the tapered portion to enter without hitting the dome of the bladder The outside of the whip catheters are routinely lubricated as customary Urethral dilatation is further facilitated in boys by introducing small amounts of lubricating jelly into the urethra before each catheter is passed

This new type of whip catheter has proven satisfactory in pediatric use for dilatation of the urethra and the external urinary meatus after meatotomy, for obtaining catheterized specimens and for instilling medications

1328 Medical Arts Bldg , Houston, Texas

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EFFECT OF GANTRISIN ON THE PROTHROMBIN TIME

ANTHONY V. PISCIOTTA, JEAN E. HINZ AND JOHN S. HIRSCHBOECK

From the Medical Service, Marquette University School of Medicine, Milwaukee County General Hospital, Milwaukee, Wis.

Although there are more than one hundred references in the literature to the use of Gantrisin, there is, to the best of our knowledge, no published study on the possible effect of this drug on prothrombin in man. Kapnick, et al.[1] reported in 1942 that about 21 per cent of their patients demonstrated a significant hypoprothrombinemia following sulfonamide administration. In this study, hypoprothrombinemia was attributed to liver damage which the authors associated with sulfonamide administration. Although the prothrombin time was increased within a few days following the institution of therapy, it reverted to normal on the administration of vitamin K. In no instance in Kapnick's series was hypoprothrombinemia severe enough to result in hemorrhage. It has been suggested[2, 3] that the reason for sulfonamide induced hypoprothrombinemia might be sterilization of the intestinal tract by these drugs. Since part of the available vitamin K is manufactured in the intestinal tract by the normal microbial flora, it is conceivable that elimination of the bacterial population, especially in poorly nourished individuals, might result in an increase of the prothrombin time.

In view of these observations and the widespread current use of Gantrisin, a preliminary study was established to determine if the administration of Gantrisin affected prothrombin in man.

METHODS

Eight patients were selected from the chronic disease wards as subjects for the study. They had been hospitalized some time previously because of multiple sclerosis, paraplegia or carcinoma. Individuals with chronic liver disease were excluded from the study. Four grams of Gantrisin were given daily in divided doses for at least three weeks. Fluids were administered *ad libitum* and alkali was not given concomitantly.

Four patients were obtained from the Urology Service and their prothrombin times determined after varying periods during which they had received 2 gm. Gantrisin daily.

One patient, F. S., was taken from the Urology Service where he had received 17 days of Gantrisin therapy, 2 gm. daily, and placed in the study group where he received 4 gm. per day for 28 days with prothrombin times determined at weekly intervals.

The ages of the patients studied ranged from 45 to 83, the average being 67.2

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[1] Kapnick, D., Stewart, J. D., and Lyons, C.: New Eng. J. Med., **227**: 944, 1942.

[2] Quick, A. J.: Amer. Pract. **3**: 397, 1952.

[3] Wintrobe, M. M.: Clinical Hematology, Philadelphia: Lea & Febiger, 1951, ed. 3, p. 253.

TABLE 1 *Relation of Gantrisin to prothrombin time*

CASE	SEX	AGE	GANTRISIN TOTAL GIVEN (GMS)	NO OF DAYS OF GANTRISIN ADMINISTRATION												
				0	7	14	17	21	24	28	31	33	38	43	45	53
				Prothrombin Time (Seconds)												
J A	M	82	84	11 8	12 5	12 5		12 0								
F S	M	48	146				13 0		12 5		13 0		12 0		11 8	
F K	M	69	84	12 5	13 0	13 5		12 0								
W R	M	52	112	12 5	13 0	12 5		12 3		12 0						
G G	M	59	84	12 8	12 8	12 0		11 5								
J S	M	82	84	12 0	12 8	12 5		12 8								
G W	M	69	84	13 0	13 3	13 5		12 5								
E H	M	64	84	12 0	12 3	13 0		11 5								
B W	F	65	84	12 0	11 8	12 5		12 0								
M T	F	83	56							12 5						
A F	F	73	66									12 8				
M L	F	82	86											14 0		
P T	M	45	106													11 5
Average		67 2	89 2	12 3	12 7	12 7		12 1								

years It was felt that the advanced age of this group and their clinical condition would provide a rigorous trial

The one stage method of Quick[4] was employed for the determination of prothrombin time The prothrombin times were determined prior to the administration of Gantrisin and at weekly intervals following the start of the experiment In addition, the patients were observed clinically for the development of hemorrhagic tendencies

RESULTS

The data obtained are summarized in table 1 The duration of treatment ranged from 21 to 53 days with an average of 29 days The total amount of Gantrisin administered varied from 56 to 146 gm , the average being 89 2 gm

The prothrombin times were 11 5 to 14 0 seconds in the group as a whole In no individual instance nor in the averages were there any indications of hypoprothrombinemia as a result of therapy with Gantrisin

DISCUSSION

The data obtained in this study failed to indicate any effect of Gantrisin upon the prothrombin time Furthermore, extensive use of the drug in this hospital has never been associated with any hemorrhagic manifestations Whether or not this complication of therapy with Gantrisin can occur as a matter of individual idiosyncrasy is a question for speculation

The synthesis of prothrombin in vivo is a complex process which involves many variables The dietary status of the patient, liver or kidney damage, defective bile drainage and disturbances in absorption from the intestinal tract are all factors which must be taken into account, either singly or collectively, in the etiologic investigation of hypoprothrombinemia. For these reasons, patients were selected who had normal control prothrombin times and who were free of any clinical condition that could contribute to hypoprothrombinemia. In this way it was felt that any diminution that might occur in the prothrombin level could be attributed to Gantrisin alone.

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[4] Quick A J The Physiology and Pathology of Hemostasis Philadelphia Lea & Febiger 1951

The difference in activity between the older sulfonamides and Gantrisin as regards prothrombin might well represent differences in toxicity between the older and the new drug or differences of their action upon the intestinal flora. Although no attempt was made to investigate this point, it is worthy of consideration.

SUMMARY

A controlled study of eight elderly and chronically ill patients failed to show any effect of Gantrisin on prothrombin times.

Five patients who received Gantrisin for 28 to 53 days for the treatment of urinary tract infections had normal prothrombin levels at the end of Gantrisin therapy.

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Western Section—*Hotel del Coronado, Coronado, Calif , January 24–27, 1955*
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